Friedländer Condensation of 1*H*-Pyrazolin-5-ones with *o*-Aminobenzaldehydes. Synthesis of 1*H*-Pyrazolo[3,4-*b*]quinolines

Danuta Tomasik and Piotr Tomasik*

Department of Chemistry and Physics, The Hugon Kołłątaj Academy of Agriculture, 30059 Cracow, Poland

Rudolph A. Abramovitch

Department of Chemistry and Geology, Clemson University, Clemson, SC 29631

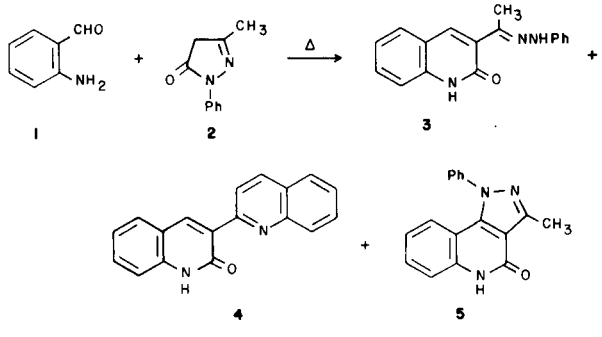
Received April 1, 1983

All the possible 1- and 3-monomethyl, monophenyl, dimethyl, diphenyl, and methylphenyl-1*H*-pyrazolin-5-ones have been condensed with *o*-aminobenzaldehyde. In some cases (but not all) 1-*H*-pyrazolo[3,4-*b*]quinolines (**10**) are formed together with a variety of other products. The balance between formation of hydrazone **11** and the ring-closed **10** is discussed, as is the formation of other products obtained in these condensations.

J. Heterocyclic Chem., **20**, 1539 (1983).

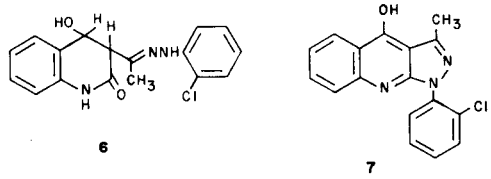
Pyrazolo[3,4-*b*]quinolines are of interest as possible antiviral agents inducing the formation of interferon [1-6]. 4-Chloro-1,3-dimethylpyrazolo[3,4-*b*]quinoline exhibits parasiticidic properties [7,8], and some 1,3-dimethylpyrazolo[3,4-*b*]quinolines were studied as potential antimalarials [9,10]. In addition, several members of this ring system fluoresce and have been proposed as optical brightners for acetate and polyester fibers [11,12].

In principle, the simplest route to pyrazolo[3,4-*b*]quinolines would be the Friedländer condensation of an *o*-aminobenzaldehyde with the desired pyrazolin-5-one. In practice, this reaction has led to a variety of products which may or may not have included the desired pyrazoloquinoline. For example, condensation of *o*-aminobenzaldehyde (**1**) with 3-methyl-1-phenylpyrazolin-5-one (**2**) [13,14] gave 3-acetylcarbostyril phenylhydrazone (**3**), 3-(2-quinolyl)carbostyril (**4**), and 3-methyl-1-phenylpyrazolo[4,3-*c*]-1*H*-quinolin-2-one (**5**). When **3** was heated with nitrobenzene cyclization to 3-methyl-1-phenylpyrazolo[3,4-*b*]quinoline occurred. On the other hand, heating **1** with 1-*o*-chlorophenyl-3-methylpyrazolin-5-one at 150° was reported to give **6** and



1 **2** **3** **4** **5**

7 [13]. Alternatively, **3** was condensed with *o*-nitrobenzaldehyde: reduction and thermal cyclization gave the desired pyrazoloquinoline [15], a procedure similar to that used in the synthesis of an indolinoquinoline [16]. Other

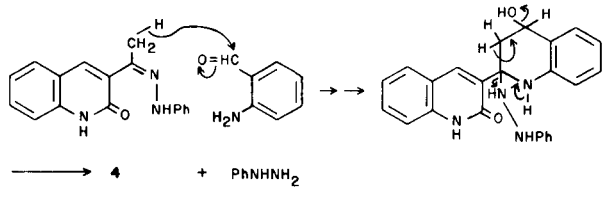


6 **7**

routes to the pyrazolo[3,4-*b*]quinoline system are available [17-22]. A 2*H*-pyrazolo[3,4-*b*]quinoline has been prepared by a Vilsmeier-Haack formylation of 5-(*p*-chloroanilino)-2-phenylpyrazolin-5-one [23].

We now report a systematic study of the condensation of **1** with 1*H*-pyrazolin-5-one itself and with its methyl-, phenyl-, dimethyl-, diphenyl-, and methyl phenyl derivatives in an effort to determine the electronic factors and to establish which ones will lead to pyrazoloquinolines and which ones will not.

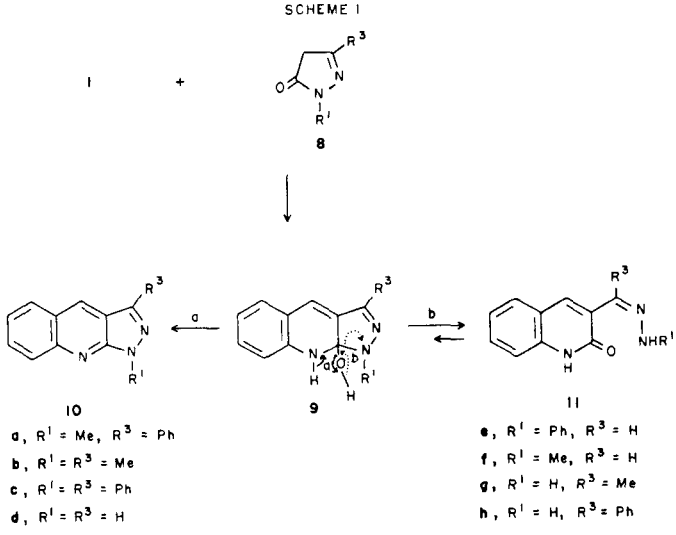
The observations of Niementowski and coworkers [13] were first confirmed in that condensation 3-methyl-1-phenylpyrazolin-5-one (**2**) with **1** at 150° gave **3** (80%), together with traces of **4**. The formation of **3** is facile as indicated by the fact that the same yield was obtained when **1** and **2** were boiled in benzene. The *o*-aminobenzylidene derivative was never isolated. When the reaction was carried out at 260° the yield of **3** dropped to 20% while that of **4** rose to 20-25%. In addition, phenylhydrazine (17%) was obtained. No **5** was isolated, but that may only be due to some differences in reaction conditions (see below for reaction with 1,3-diphenylpyrazolin-5-one). That **4** arises from **3** was shown readily by heating **3** with **1** at 260° for 15 minutes to give **4** (20%).



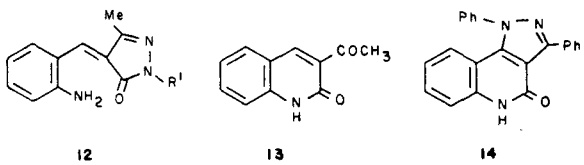
→ **4** + $PhNHNH_2$

On the other hand, when 1-methyl-3-phenylpyrazolin-5-one (**8a**) was used the only product formed at 150° (98% yield) was 1-methyl-3-phenyl-1*H*-pyrazolo[3,4-*b*]quinoline (**10a**). No visible reaction took place between **1** and **8a** in boiling benzene. Thus, the intermediate **9** either loses water (to give **10**) (pathway *a*, Scheme 1) or undergoes ring opening (to give **11**) (pathway *b*, Scheme 1) based largely on the nature of the substituents in **8**. One would expect that

SCHEME 1



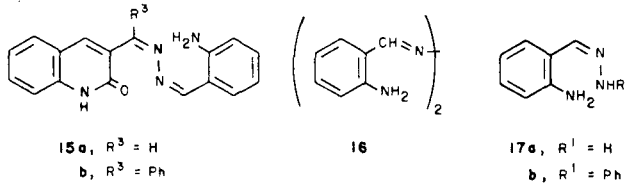
substituents on N_1 of the pyrazole ring that can delocalize a pair of electrons would favor ring opening (path *b*), while those that do not would favor dehydration (path *a*) and, to that extent, compounds **2** (N_1-Ph) and **8a** (N_1-Me) behave predictably. The substituent at C_3 of the pyrazole does play a key role, however, as indicated by the behavior of **8b** ($R^1 = R^3 = Me$) and **8c** ($R^1 = R^3 = Ph$). Thus, when **8b** ($R^1 = R^3 = Me$) and **1** were heated at 150° a good yield (70%) of the benzylidene derivative (**12**) ($R^1 = Me$) was obtained, together with a small amount (8%) of 3-acetylcarbostyril (**13**). The latter could arise from **11** ($R^1 = R^3 = Me$) during the purification process. At 260°, both paths *a* and *b* seem to be followed to about the same extent, with **10b** ($R^1 = R^3 = CH_3$) and **4** being obtained in 20% yield each. When **12** ($R^1 = Me$) was heated to 260° a quantitative yield of **10b** was formed. The substituents are thus influencing not only the rate of attack of the carbonyl group by the amino function but also the subsequent steps (paths *a* or *b*--Scheme 1). It would appear from these results as though a 3-methyl group facilitates ring-opening (path *b*) while a 3-phenyl group (as in **8a**) facilitates dehydration (path *a*), though the balance between the



substituents effects from N_1 and C_3 is not clear at all. Indeed, our subsequent experiments (particularly when $R^1 = H$ and $R^3 = Me$ *or* Ph in **8**) cast serious doubt on such a generalization.

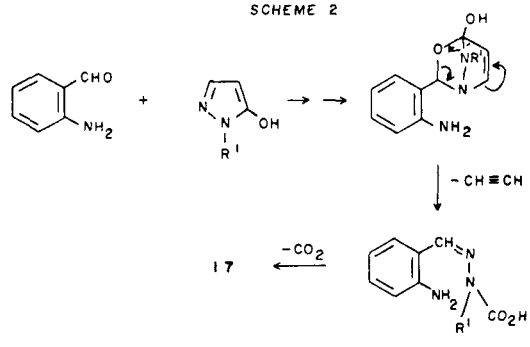
When 1,3-diphenylpyrazolin-5-one (**8c**) is heated with **1** at 200° the main product (68%) is **10c** ($R^1 = R^3 = Ph$), suggesting that the 3-Ph group is exerting the dominant electronic effect in this case. The phenylhydrazine **11c** ($R^1 = R^3 = Ph$) is obtained in only 5-7% yield and some 1,3-diphenyl-2*H*-pyrazolo[4,3-*c*]-1*H*-quinolin-2-one (**14**) (15%) was also formed. On the other hand, when the reaction is carried out at 150° only traces of **10c** were detected, the main product being **11c** (79%), together with **14** (15%). Phenylhydrazone **11c** is stable to atmospheric oxygen at room temperature for several months and at its melting point for several hours. A possible explanation for the formation of **14** is that the oxidative cyclization of **11c** (and, presumably, of **3**→**5**) is mediated by excess *o*-aminobenzaldehyde. Thus, when **11c** was heated with boiling nitrobenzene it gave **14** (82%).

1*H*-Pyrazolinone (**8d**) itself gave no pyrazolo[3,4-*b*]quinoline. Instead, *o*-aminobenzaldazine (**15a**) (10%) and 2,2'-diaminobenzaldazine (**16**) (40%) were obtained. Compound **15a** undoubtedly arises from reaction of **11d** ($R^1 = R^3 = H$) (formed by path *b*) with unchanged *o*-aminobenzaldehyde (**1**) while **16** appears to be formed from *o*-aminobenzaldehyde hydrazone (**17a**) (see below). Compound **8e**



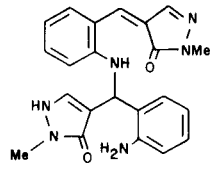
($R^1 = Ph$, $R^3 = H$), on the other hand, gave a virtually quantitative yield of *o*-aminobenzaldehyde phenylhydrazone (**17b**). Acetylene was also formed in this reaction and trapped as copper acetylide. A possible mode of formation of **17** is shown in Scheme 2 (formation of the proposed bridged (4 + 2) adduct may well be a stepwise process).

SCHEME 2



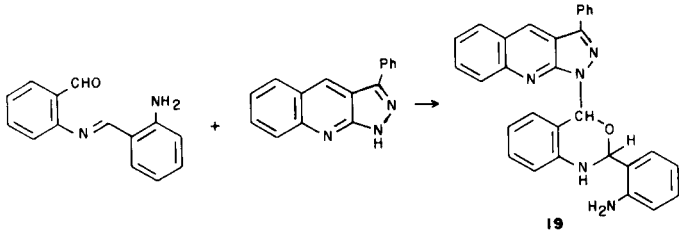
The reaction of **8f** took yet a different path, yielding a dimer of 4-*o*-aminobenzylidene-1-methylpyrazolin-5-one

(70% yield) [M⁺, m/e 402 (55%), 201 (40%), 304 (98%, M⁺-$C_4H_6N_2O$)] for which we tentatively propose structure **18**, based mainly on the mass, infrared [3485, 3350, 3285, 3130 cm^{-1} (NH_2, NH), 1660 cm^{-1} (α, β unsaturated C=O)] and nmr (1H singlets at δ 4.45 and 4.25 attributed to NH-C*H*=C-CO and NH-C*H*(Ar)-C=C, respectively] spectra of the compound.



18

Pyrazolinene **8g** behaved somewhat more predictably, yielding **10** (R^1 = H, R^3 = Me) (73%) at 150°, together with **12** (R^1 = H) (6%) and **16** (5%). 1*H*-3-Phenylpyrazolin-5-one (**8h**) also gave the desired pyrazolo[3,4-*b*]quinoline (**10**, R^1 = H, R^3 = Ph) (43%), together with a product (**19**) (20%) whose (very tentatively) proposed structure is *formally* derived from a nucleophilic addition of **10** (R^1 = H, R^3 = Ph) to the self-condensation product of **1** (stepwise processes involving one molecule of **1** at a time are most likely). In support of structure **19** (or related one) is its



19

mass spectrum (M⁺, 469) and a fragment at M⁺ - 244 (*i.e.* minus the 3-phenylpyrazoloquinoline moiety), the absence of a carbonyl band in the infrared, and 1H singlets at δ 5.67 and 5.62. Much further work is needed to establish the correct structure of this compound. A possible precursor to **19** was also isolated, namely the aldazine (**15b**) (8% yield) resulting from the condensation of 3-benzoylcarbostyril hydrazone with **1**.

In conclusion, one can say that the Friedländer synthesis can provide direct access to some 1*H*-pyrazolo[3,4-*b*]-quinolines, and indirect access of others *via* carbostyril derivatives **11** by heating them in nitrobenzene (**13**). Many byproducts are formed, however, some of uncertain structure, and the effects of methyl and phenyl substituents in the parent pyrazolone on the nature of the products is still not rationalized. With **8d, e**, and **f** none of the desired products were formed.

EXPERIMENTAL

1*H*-Pyrazolin-5-ones.

These were all known compounds and were made by the literature procedures: 1*H*-pyrazolin-5-one [24], 1,3-dimethyl- [25],, 2,3-diphenyl- [26], 3-methyl-1-phenyl- [27], 1-methyl-3-phenyl [28], 1-phenyl- [29], 1-methyl-[30], 3-phenyl- [31], and 3-methylpyrazolin-5-one [32].

Condensation of 1*H*-Pyrazolinones with *o*-Aminobenzaldehyde. General Procedure.

Equimolar amounts of the pyrazolinone and *o*-aminobenzaldehyde were ground together and heated either at 150°, 200° or 260°. Foaming resulted on fusion and intense blue, red, violet, purple, or orange colors appeared, depending on the pyrazolinone used. When no more gases were evolved heating was discontinued and the yellowish grey solid fractionally crystallized from polar solvents. For the parent pyrazolinone and its monosubstituted derivatives separation was best effected on silica gel columns (Merck 40, 70-230 mesh) using the same solvents as were found to give separation on TLC plates consisting of an 0.2 mm layer of Merck silica gel 60 (F 254).

Products from 1*H*-Pyrazolin-5-one (**8d**).

The reaction was carried out at 150°. Elution with benzene:chloroform:ethanol (5:5:1 v/v) gave aldazine **15a** (10%), mp 265°; ir (potassium bromide): 3410, 3290 (NH_2), 1670 cm^{-1} (C=O); nmr (DMSO-d_6): δ 9.20 (s, H, -CH=N-), 8.80 (s, 1H, Hγ), 7.60-7.30 (m, 4H), 7.15-6.99 (m, 4H); ms: m/e 290 (M⁺).

Anal. Calcd. for $C_{17}H_{14}N_4O$: C, 70.34; H, 4.83; N, 19.31. Found: C, 70.40; H, 4.91; N, 19.33.

Further elution gave 2,2'-diaminobenzaldazine (**16**) (40%), mp 244° (lit mp 244° [33]); ir (potassium bromide): 3540, 3430 cm^{-1} (NH_2); nmr (DMSO-d_6): δ 8.95 (s, 2H), 7.45 (t, 4H), 6.90 (t, 4H); ms: m/e 238 (M⁺).

Anal. Calcd. for $C_{14}H_{14}N_4$: C, 70.59; H, 5.88; N, 23.53. Found: C, 70.44; H, 5.99; N, 23.24.

Products from 1-Phenylpyrazolin-5-one (**8e**).

An almost quantitative yield of *o*-aminobenzaldehyde phenylhydrazone (**17b**), mp 220° (lit mp 221° [34]) was obtained by chromatography of the reaction mixture on silica gel and elution with benzene:ethanol (9:1 v/v); ir (potassium bromide): 3465, 3410, 3300 cm^{-1} (NH_2); ms: m/e 211 (M⁺).

Anal. Calcd. for $C_{13}H_{13}N_3$: C, 73.93; H, 6.16; N, 16.41. Found: C, 73.99; H, 6.27; H, 16.60.

Products from 1-Methylpyrazolin-5-one (**8f**).

The reaction was carried out at 150°. Elution of the column with benzene:chloroform:ethanol (4:3:1 v/v) gave the dimer of 4-*o*-aminobenzylidene-1-methylpyrazolin-5-one (**18**) (70%), mp 183°; ir (potassium bromide): 3485, 3350, 3285, 3130 (NH_2, NH), 1660 cm^{-1} (C=C-C=O); nmr (DMSO-d_6): δ 7.15-6.15 (m, 11H), 4.45 (s, 1H), 4.25 (s, 1H), 3.46 (s, 6H); ms: m/e 402 (M⁺).

Anal. Calcd. for $C_{22}H_{22}N_6O_2$: C, 65.67; H, 5.47; N, 20.90. Found: C, 65.78; H, 5.61; N, 20.99.

This compound gradually decomposes when heated to 260°.

Products from 3-Methyl-1*H*-pyrazolin-5-one (**8g**).

The reaction was carried out at 150°. Elution with benzene:chloroform:ethanol (8:3:4 v/v) gave 2,2'-diaminobenzaldazine (**16**) (5%), mp 244°, identical with an authentic sample prepared from *o*-aminobenzaldehyde and hydrazine. Further elution with the same solvent gave 1*H*-3-methylpyrazolo[3,4-*b*]quinoline (**10g**) (74%), mp 252°; ir (potassium bromide): 3280 cm^{-1} (NH); nmr (DMSO-d_6): δ 8.82 (s, 1H), 7.5-6.5 (m, 4H), 3.4 (s, 4H, C*H*$_3$, NH); ms: m/e 183 (M⁺). The compound exhibited strong greenish yellow fluorescence in solution.

Anal. Calcd. for $C_{11}H_9N_3$: C, 72.13; H, 4.91; N, 22.95. Found: C, 72.19; H, 5.02; N, 23.08.

Continued elution gave 4-*o*-aminobenzylidene-3-methyl-1*H*-pyrazolin-5-one (**12**; R^1 = H) (6%), mp 198°; ir (potassium bromide): 3480, 3405 (NH_2), 1664 cm^{-1} (C=O); ms: m/e 201 (M⁺).

Anal. Calcd. for $C_{11}H_{11}N_3O$: C, 65.67; H, 5.47; N, 20.90. Found: C, 65.73; H, 5.56; N, 21.04.

Products from 3-Phenyl-1*H*-pyrazolin-5-one (**8h**).

The reaction was carried out at 150°. Elution with benzene:ethanol (9:1 v/v) gave the aldazine **15b** (8%), mp 292°; ir (potassium bromide): 3465, 3420 (NH_2), 1647 cm^{-1} (C=O); ms: m/e 366 (100%) (M^+), 365 (39%), 350 (17%, $M^+ - NH_2$), 289 (91%, $M^+ - C_6H_5$).

Anal. Calcd. for $C_{23}H_{18}N_4O$: *M*, 366.1481. Found: *M*, 366.1479.

Further elution with benzene:ethanol (9:1 v/v) gave 1*H*-3-phenylpyrazolo[3,4-*b*]quinoline (**10h**) (43%), mp 264°, ms: m/e 245 (M^+). Solutions exhibited a greenish yellow fluorescence.

Anal. Calcd. for $C_{16}H_{11}N_3$: C, 78.36; H, 4.49; N, 17.14. Found: C, 78.45; H, 4.72; N, 16.91.

Continued elution gave a compound tentatively assigned structure **19** (20%), mp 220-221; no C=O bond in ir, nmr (DMSO-d_6) δ 7.74 (s, 1H), 7.50-6.57 (m, 17H), 5.67 (s, 1H), 5.62 (s, 1H); ms: m/e 469 (M^+).

Anal. Calcd. for $C_{30}H_{23}N_5O$: C, 76.76; H, 4.90; N, 14.93. Found: C, 76.95; H, 4.88; N, 15.07.

Products from 3-Methyl-1-phenylpyrazolin-5-one (**2**).

The reaction was carried out at 150°. Chromatography on silica gel and elution with benzene:acetic acid (10:3 v/v) gave 3-acetylcarbostyril phenylhydrazone (**3**) (80%), mp 232° (lit mp 232° [13]); ir (potassium bromide): 1654 cm^{-1} (C=O); nmr (DMSO-d_6): δ 8.47 (s, 1H), 7.44 (m, 8H), 2.46 (s, 3H, CH_3); ms: m/e 277 (M^+).

Anal. Calcd. for $C_{17}H_{15}N_3O$: C, 73.65; H, 5.42; N, 15.16. Found: C, 73.71; H, 5.45; H, 15.25.

Also isolated before **3** was a trace of 3-(2-quinolyl)carbostyril (**4**), mp 324° (from glacial acetic acid); ir (potassium bromide): 1655 cm^{-1} (C=O); nmr (trifluoroacetic acid): δ 9.60 (s, 1H), 9.01 (d, 1H, J = 4 Hz), 8.93 (d, 1H, J = 4 Hz), 8.00 (m, 8H); ms: m/e 272 (M^+).

Anal. Calcd. for $C_{16}H_{12}N_2O$: C, 79.41; H, 4.41; N, 10.29. Found: C, 79.30; H, 4.60; N, 10.38.

When the reaction was carried out at 260°, a 20% yield of **3** and a 20-25% yield of **4** were isolated. The reaction was repeated at 260° under a reflux condenser, the final reaction mixture, condenser, and flask were washed with 5% hydrochloric acid, the solid was filtered and the filtrate was concentrated until a crystalline solid began to separate. The precipitate was filtered and dried (17% yield) and shown to be identical (mp, ir) with an authentic sample of phenylhydrazine hydrochloride, mp 244-246° (lit mp 243-246° [35]).

When equimolar amounts of **2** and **1** (0.02 mole) in benzene (100 ml) were heated under reflux with, or without, Molecular Sieve only **3** (80%) was isolated.

Products from 1-Methyl-3-phenylpyrazolin-5-one (**8a**).

When the reaction was carried out at 150°, 1-methyl-3-phenylpyrazolo-[3,4-*b*]quinoline (**10a**) (98%), mp 149°, was obtained; ir (potassium bromide): no C=O absorptions; nmr (trifluoroacetic acid): δ 9.03 (s, 1H), 8.08 (m, 9H), 4.53 (s, 3H, Me); ms: m/e 259 (M^+). Solutions of the compound exhibit strong green fluorescence.

Anal. Calcd. for $C_{17}H_{13}N_3$: C, 78.76; H, 5.02; N, 16.22. Found: C, 78.70; H, 5.13; N, 16.01.

Products from 1,3-Dimethylpyrazolin-5-one (**8b**).

When the reaction was carried out at 150° the following products were isolated: 4-*o*-Aminobenzylidene-1,3-dimethylpyrazolin-5-one (**12**, R^1 = Me) (70%), mp 197°; ir (potassium bromide): 3560, 3450 (NH_2), 1678 cm^{-1} (C=O); nmr (trifluoroacetic acid): δ 7.55 (m, 4H), 5.54 (s, 1H), 3.64 (s, 3H, Me), 2.02 (s, 3H, Me); ms: m/e 215 (M^+).

Anal. Calcd. for $C_{12}H_{13}N_3O$: C, 66.98; H, 6.05; N, 19.53. Found: C, 66.78; H, 6.19; N, 19.70.

The compound appears to dimerize when kept in pyridine for 3 days at room temperature.

3-Acetylcarbostyril (**13**).

This compound was obtained in 8% yield, mp 246° (lit mp 232° [36]); ir (potassium bromide): 1678 (C=O). 1653 cm^{-1} (C=O); nmr (DMSO-d_6): δ 8.60 (s, 1H), 8.1-7.1 (m, 4H), 2.66 (s, 3H, Me); ms: m/e 187 (M^+).

Anal. Calcd. for $C_{11}H_9NO_2$: C, 70.59; H, 4.81; N, 7.49. Found: C, 70.42; H, 4.86; N, 7.42.

When the reaction was carried out at 260° the products were:

1,3-Dimethylpyrazolo[3,4-*b*]quinoline (**10b**).

This compound was obtained in a yield of 20%, mp 150°; no C=O or NH bands in ir; nmr (DMSO-d_6) δ 9.02 (s, 1H), 7.96 (m, 4H), 4.25 (s, 3H, NMe), 2.84 (s, 3H, 3-Me); ms: m/e 197 (M^+). Solutions of the compound exhibited strong violet fluorescence. Compound **10b** was also obtained quantitatively when **12** (R^1 = Me) was heated at 260°.

Anal. Calcd. for $C_{12}H_{11}N_3$: C, 73.10; H, 5.58; N, 21.31. Found: C, 73.23; H, 5.70; N, 21.39.

3-(2-Quinolyl)carbostyril (**4**).

This compound was obtained in a yield of 20%, mp 324°, identical with the sample obtained above.

Products from 1,3-Diphenylpyrazolin-5-one (**8c**).

When the reaction was carried out at 200° the following were isolated.

1,3-Diphenylpyrazolo[3,4-*b*]quinoline (**10c**).

This compound was obtained in a yield of 68%, mp 167°; nmr (trifluoroacetic acid): δ 9.72 (s, 1H), 8.5-7.6 (m, 14H); ms: m/e 321 (M^+). Solutions of this compound exhibit strong blue fluorescence.

Anal. Calcd. for $C_{22}H_{15}N_3$: C, 82.24; H, 4.67; N, 13.08. Found: C, 82.40; H, 4.77; N, 13.13.

3-Benzoylcarbostyril Phenylhydrazone (**11c**).

This compound was obtained in a yield of 5.7%, mp 284°; ir (potassium bromide): 1650 cm^{-1} (C=O); nmr (trifluoroacetic acid): δ 8.45 (s, 1H), 7.95-7.0 (m, 14H); ms: m/e 339 (M^+).

Anal. Calcd. for $C_{22}H_{17}N_3O$: C, 77.88; H, 5.01; N, 12.39. Found: C, 78.01; H, 5.15; N, 12.42.

Traces of **14** were also obtained.

When the reaction was carried out at 150° the following were isolated.

3-Benzoylcarbostyril Phenylhydrazone (**11c**).

This compound was obtained in a yield of 79%, identical with the compound obtained at 200°.

1*H*-3,5-Diphenylpyrazolo[4,3-*c*]-1*H*-quinolin-2-one (**14**).

This compound was obtained in a yield of 15%, mp 324°; ir (potassium bromide): 1660 cm^{-1} (C=O); nmr (DMSO-d_6): δ 8.27 (m, 2H), 7.57 (m, 10H), 6.98 (m, 2H); ms: m/e 337 (M^+).

Anal. Calcd. for $C_{22}H_{15}N_3O$: C, 78.34; H, 4.45; N, 12.46. Found: C, 78.42; H, 4.51; N,12.70.

1,3-Diphenylpyrazolo[3,4-*b*]quinoline (**10c**).

This compound was obtained in trace amounts.

Acknowledgement.

The authors are grateful for a National Science Foundation (Excess Foreign Currency) and the Polish Fundusz Marii Sklodowskiej-Curie grant No. OIP-75-02094.

REFERENCES AND NOTES

[1] R. R. Crenshaw, G. M. Luke and P. Smirnoff, *J. Med. Chem.*, **19**, 262 (1976).

[2] P. Smirnoff and R. R. Crenshaw, *Antimicrob. Agents Chemother.*, **11**, 571 (1977); *Chem. Abstr.*, **85**, 153844d (1977).

[3] P. Smirnoff, *J. Infect. Dis.*, **133**, Suppl. (June), A, 37 (1976); *Chem. Abstr.*, **85**, 18823k (1976).

[4] R. R. Crenshaw, G. M. Luke and P. Smirnoff, Canadian Patent 1,032,538 (1978); *Chem. Abstr.*, **89**, 179995r (1978).

[5] E. G. Shcherbakova, N. M. Furer, G. A. Rastunova, A. N. Litvinov, V. E. Zhigachev and N. N. Suvorov, *Antibiotiki* (Moscow), **21**, 838 (1976).

[6] R. E. Kern, J. R. Hamilton, J. C. Overall, Jr., and L. A. Glasgow,

Antimicrob. Agents Chemother., **10**, 691 (1976); *Chem. Abstr.*, **86**, 11816x (1977).

[7] R. R. Crenshaw, G. M. Luke and P. Smirnoff, West German Patent 2,446,821 (1975); *Chem. Abstr.*, **83**, 97285W (1975).

[8] Bristol-Meyers Co., French Demande 2,149,275 (1973); *Chem. Abstr.*, **79**, 78784n (1973).

[9] T. N. Ghosh, *J. Indian Chem. Soc.*, **14**, 123 (1937).

[10] R. G. Stein, J. H. Biel and T. Singh, *J. Med. Chem.*, **13**, 153 (1970).

[11] A. Brack, Belgian Patent 617,180 (1962); *Chem. Abstr.*, **59**, 636a (1963).

[12] G. Wolfrum, R. Puetter, H. G. Hanke and K. H. Menzel, Belgian Patent 632,758 (1963); *Chem. Abstr.*, **61**, 756e (1964).

[13] A. Musierowicz, S. Niementowski and Z. Tomasik, *Rocz. Chem.*, **8**, 325 (1928).

[14] Z. Tomasik, *ibid.*, **8**, 345 (1928).

[15] K. S. Narang, J. N. Ray and A. Singh, *J. Indian Chem. Soc.*, **11**, 427 (1934).

[16] R. A. Abramovitch, R. T. Coutts and N. J. Pound, *Chem. Ind.* (London),1871 (1960).

[17] A. Kocwa, *Bull. Int. Acad. Polon, Sci., Cl. Sci. Math. Nat. A*, 266 (1936).

[18] A. Kocwa, *ibid.*, 232 (1937).

[19] A. Brack, *Ann. Chem.*, **681**, 105 (1965).

[20] G. Wolfrum, R. Puetter, H. G. Hanke and K. H. Manzel, West German Patent 1,152,421 (1963); *Chem. Abstr.*, **60**, 2945e (1964).

[21] W. J. Adams and D. H. Hey, *J. Chem. Soc.*, 1521 (1951).

[22] K. Yoshida and K. Otomasu, *Yakugaku Zasshi*, **96**, 33 (1976); *Chem. Abstr.*, **84**, 121754s (1976).

[23] V. Purnaprajna and S. Seshadri, *Indian J. Chem.*, **14b**, 971 (1976).

[24] S. Ruhemann and R. S. Morell, *J. Chem. Soc.*, **61**, 793 (1892).

[25] L. Wolff and W. Schreiner, *Ber.*, **41**, 556 (1908).

[26] L. Knorr and C. Klotz, *ibid.*, **20**, 2546 (1887).

[27] L. Knorr, *ibid.*, **16**, 2597 (1883).

[28] H. Dorn, *Ann. Chem.*, **352**, 163 (1907).

[29] H. Conrad and M. Guthzeit, *Ber.*, **15**, 2842 (1882).

[30] F. Lingens and H. Schneider-Bernloehr, *Angew. Chem.*, **76**, 378 (1964).

[31] T. Curtius, *J. Prakt. Chem.*, [2]**50**, 515 (1900).

[32] T. Curtius and J. Jay, *ibid.*, [2]**39**, 27 (1889).

[33] S. Gabriel and E. Leupold, *Ber.*, **31**, 2186 (1898).

[34] J. Eliasberg and P. Friedländer, *ibid.*, **25**, 1752 (1892).

[35] W. Autenrieth, *ibid.*, **29**, 1653 (1896).

[36] P. Friedländer and C. F. Gohring, *ibid.*, **16**, 1833 (1883).