Novel Tricyclic Heterocycles (Benzopyrrocolines) Arising *via* Carbanion Attack on a Nitrile Function

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A new reaction of 2-*n*-alkanoyl-1,2-dihydroisoquinaldonitriles **1** (isoquinoline Reissert compounds) has been discovered. As previously reported reaction of the conjugate bases of Reissert compounds with alkyl halides yields the corresponding 1-alkyl derivatives **2**. However, compounds **2**, R = *n*-alkyl, with only a catalytic amount of bases form the enolate ion, which attacks the neighboring nitrile functionality to produce directly in the same reaction vessel excellent yields of benzopyrrocoline derivatives **5-10**. The nmr spectrum reveals a solvent dependent tautomeric equilibrium between ketoeneamine (**a**) and ketoimine (**b**) forms. Unlike compounds **2** the double bonds of the pyridine ring of compounds **7** and **8** were readily reduced with hydrogen. Thus, *n*-alkanoyl Reissert compounds afford a convenient route to the corresponding benzopyrrocolines.

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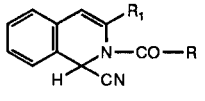
Isoquinoline Reissert compounds [1,2] (2-acyl-1,2-dihydroisoquinaldonitriles **1**) provide access to a number of interesting and useful isoquinoline derivatives. Alkylation *via* the anions is well known [1-3]; it yields the 1-alkylisoquinoline following hydrolysis. This process has seen use in the synthesis of a number of alkaloids [4,5]. In general these reactions are high yield processes, at least in the cases of the *N*-aroyl compounds **1**, R = aryl. However, in the course of synthesis of some 1-alkyl-2-alkanoyl derivatives **2**, R = alkyl from **1**, R = alkyl in connection with stereochemical studies [6,7] low yields were encountered and in some cases in spite of variation in experimental conditions another product dominated. The present paper describes the characterization of the reaction products.



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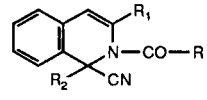
a, R = CH_3, R_1 = H



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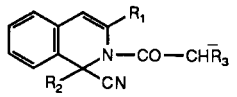
a, R = CH_3, R_1 = H, R_2 = i-C_3H_7
b, R = C_2H_5, R_1 = H, R_2 = i-C_3H_7

Discussion.

When alkanoyl Reissert compounds of type **1**, R = *n*-alkyl are alkylated in the presence of one or more equivalents of base (sodium hydride) high melting compounds isomeric to **2** are formed in good yields. However, branched alkanoyl Reissert compounds, such as **1**, R = $CH(CH_3)_2$, do not undergo the anamolous reaction, but instead form the expected **2** in high yields.



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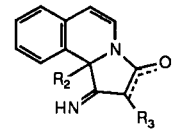

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Enolate **3** can cyclize intramolecularly *via* attack of the carbanion on the nitrile function to form **5-10** in three tautomeric forms. As described below the product structures are consistent with all of the spectral data.

Several compounds were prepared, some directly from compounds **1** and some *via* compounds **2**. These are listed

Table 1

Tricyclic Compounds

Compound	MP [a]	Yield	Calcd./(Found) %C	%H	%N
5 [b]	251.5-2.5 [c]	72	74.97 (75.06)	6.71 (6.73)	11.66 (11.67)
6 [d]	272.0-3.5	85	75.56 (75.31)	7.13 (7.25)	11.02 (11.18)
6 [b]		83	—	—	—
7 [d]	282.5-4.0	71	75.56 (75.59)	7.13 (7.22)	11.02 (11.04)
8 [d]	323-5 [e]	44	75.56 (75.97)	7.13 (7.21)	11.02 (11.03)
9 [d]	255.5-6.5 [f]	62	76.08 (75.88)	7.51 (7.61)	10.44 (10.49)
10 [d]	195.0-6.0 [g]	87	79.44 (79.53)	6.9 (6.07)	9.27 (9.40)
11 [h]	212.3-5.0 [i]	89	74.96 (74.87)	7.86 (7.98)	10.93 (10.64)
12 [h]	291.0-3.0 [f]	89	74.96 (75.35)	7.86 (7.68)	10.93 (10.88)

[a] Recrystallized from ethanol unless otherwise noted. [b] *Via* isolated 1-alkyl derivative. [c] From ethanol-water. [d] Directly from Reissert compound and alkyl halide. [e] Insoluble, purified by washing with boiling ethyl acetate, then boiling ethanol. [f] From ethanol-ethyl acetate. [g] Recrystallization from hexane-ethyl acetate gave colorless crystals of same mp but containing one mole of ethyl acetate; ^{1}H nmr (perdeuterioacetic acid): t, δ 1.24; s, δ 2.06; q, δ 4.17). *Anal.* Calcd. for $C_{24}H_{26}N_2O_3.CH_3COOC_2H_5$: C, 73.82; H, 6.71; N, 7.18. Found: C, 73.84; H, 6.60; N, 7.29. [h] Reduction of corresponding unsaturated compound. [i] From ethyl acetate-hexane.

in Table 1. All of these compounds are high melting and of limited solubility in organic solvents. As noted above, branching α to the carbonyl group of **1** prevents the reaction, presumably because of the lack of stabilization of the product by enolate tautomer **4**, just as in the Claisen condensation where such product stabilizaton is required [11].

The nmr spectrum of the product **5** in DMSO-d_6 (Figure 1a), besides the isopropyl and isoquinoline proton signals in the proper ratio, contains signals at δ 3.50 (H_2O), δ 4.90 (s, 1H) and δ 7.3 (2H). The peak at δ 4.90 is assigned to proton R_3 of tautomer **5a**; as a point of reference the vinyl proton of methyl 3-amino-2-butenoate appears at δ 4.53 [8]. The singlet in the low field signal (δ 7.3) is assigned to the NH_2 group of **5a**. Tautomers **5b** and **5c** were not detected. However, when the spectrum was recorded in perdeuterioacetic acid (Figure 1b), the signal at δ 4.90 (1H) dissappeared and a peak at δ 2.40 (2H) appeared. Additionally the signal under the aromatic protons moved upfield to δ 6.82 (1H). The δ 2.40 signal is assigned to the geminal H_y and R_3 protons of tautomer **5b** and that at δ 6.82 to the imino proton of **5b**. Thus, by changing from a strongly hydrogen bonding to a weakly hydrogen bonding solvent, complete conversion from one tautomeric form **5a** to another **5b** was incurred as reported for other enamines [9]. The absence of a signal for an enol proton, which would be separate from the imino protons in acetic acid [10a], rules out the presence of tautomer **5c**. Further, heating of the perdeuterioacetic acid solution to 70° (Figure 1c) resulted in loss of both the signal at δ 6.82 (=NH) and the one at 2.40 ($COCH_2$) and appearance of a signal at δ 10.8. Complete exchange of deuterium for hydrogen occurred as reported for other imines [9]. Confirmation of the assignment of the δ 7.3 peak in DMSO-d_6 as the NH_2 of **5a** (Figure 1a) was made by examination of the spectrum of **6** in DMSO-d_6. An analogous NH_2 signal present at δ 7.22 disappeared upon addition of a drop of deuterium oxide. The relevant parts of the ^1H nmr spectra are summarized in Table 2. In DMSO all the compounds exist in tautomeric form **a**.

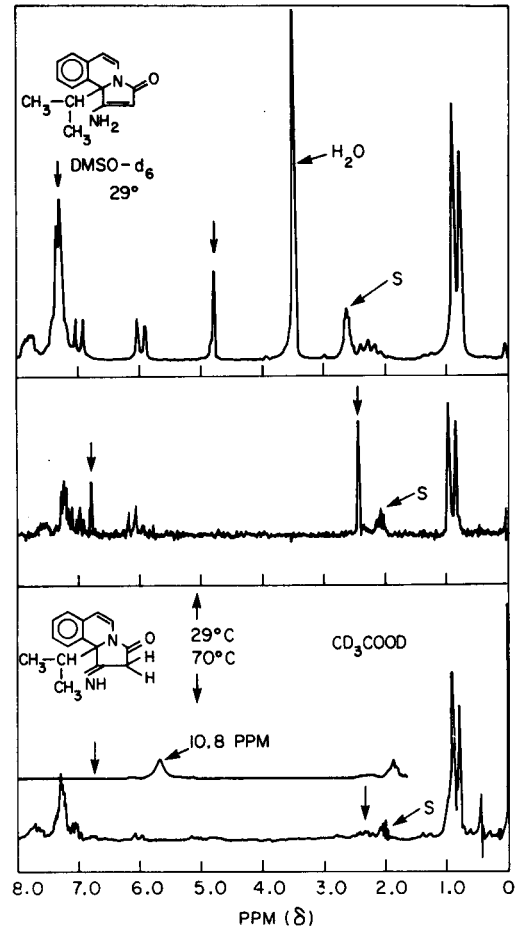
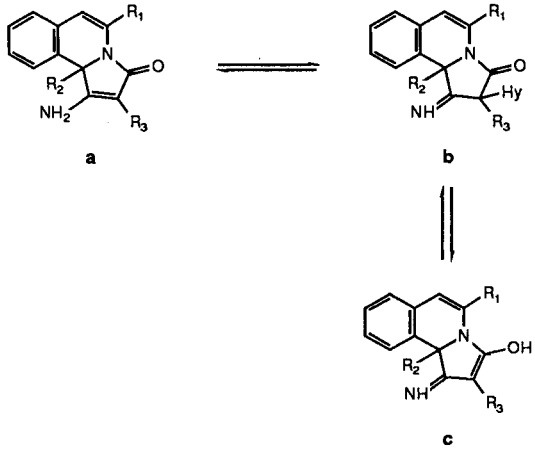


Figure 1. Proton nmr spectra of **5**. a) top in DMSO-d_6 at 29°; b) middle, in perdeuterioacetic acid at 29°; and c) bottom, in perdeuterioacetic acid at 70°. Signals labelled "S" are due to protonated solvent impurities. Vertical arrows mark peaks which appear or disappear.



Compound	R_1	R_2	R_3
5	H	$CH(CH_3)_2$	H
6	CH_3	$CH(CH_3)_2$	H
7	H	$CH(CH_3)_2$	CH_3
8	CH_3	C_2H_5	CH_3
9	CH_3	$CH_2CH(CH_3)_2$	H
10	CH_3	$CH_2C_6H_5$	H

The ultraviolet spectra of several of these compounds were recorded (Table 3) and all showed two intense long wavelength bands. The presence of a methyl group at R_1 decreases λ max by 10 nm. The λ max values for **5** shift to shorter wavelengths by 4-6 nm when the solvent is changed from DMSO to acetic acid, consistent with conversion from form **a** to less conjugated **b**.

When **7** and **8** were catalytically reduced, one mole of hydrogen was absorbed in each case, yielding **11** and **12**, respectively. Compounds of types **1** and **2** are not reduced under these conditions. The two long wavelength uv bands associated with the styrene chromophore disappeared (Table 3). The nmr spectrum of **11** in perdeuterioacetic

Table 2

^{1}H NMR Spectra of Tricyclic Compounds [a]

Compound	Solvent [b]	Chemical Shifts (δ, ppm) R_3	NH	R_1	H_4
5a	DM	4.90 (s)	7.3 (b)	7.00 (d, J = 7.5)	5.98 (d, J = 7.5)
5b	DA	2.40 (s)	6.82 (s)	7.08 (d, J = 8)	6.15 (d, J = 8)
5b	DA [c]	--	10.8 (s)	7.08 (d, J = 8)	6.15 (d, J = 8)
6a	DM	4.72 (s)	7.1 (s)	2.36 (d, J = 1.5)	5.86 (q, J = 1.5)
7a	DM	1.63 (s)	6.8 (b)	6.98 (d, J =8)	5.93 (d, J = 8)
9a	DM	4.74 (s)	7.2 (s)	2.37 (d, J = 2)	5.92 (q, J = 2)
11a	DA	1.59 (s)	11.22 (s)	2.1-3.2 (m)	[d]

[a] At 29° unless otherwise noted. [b] DM = DMSO-d_6; DA = perdeuterioacetic acid. [c] At 70°. [d] Axial (?) in multiplet at δ 2.1-3.2; equatorial (?); multiplet at δ 4.

Table 3

Ultraviolet Spectra [a]

Compound	λ max (nm) / ε × 10^{-3}				
2a	328 sh/3.25	313 sh/7.33	296/8.78	2.33 sh/13.2	227/15.8
2b	322 sh/3.71	307 sh/7.39	293/9.91	233 sh/11.6	226/14.6
5	343/5.38	306/3.74	265/33.0	218/25.9	
5 [b]	344/4.65	311 sh/2.74	269/26.1		
5 [c]	340/4.65	307 sh/2.51	263/28.6		
6	333/5.16		306/4.47	264/36.9	219/6.91
7	345/4.56	306/2.93	268/27.3	218/22.6	
8	336/5.24	308 sh/3.54	266/34.2	219/26.2	
10	334/3.96	305/2.62	265/25.3	217/24.9	
11			273/5.50	215 sh/12.0	
12			274/9.98	213 sh/23.2	

[a] Unless otherwise noted solvent is absolute ethanol. [b] Solvent: dimethyl sulfoxide. [c] Solvent: acetic acid.

Compound	R_1	R_2
11	H	$CH(CH_3)_2$
12	CH_3	C_2H_5

acid confirmed loss of the easily recognized set of doublets due to protons of 3,4-double bond of **7**. The methyl signal of **11** was unsplit; this rules out the structure analogous to **7b**. To distinguish between possible tautomers **11a** and **11b** use was made of the fact [10a] that in perdeuterioacetic acid enolic OH protons can be seen separately from amino and imino protons. In fact only a single downfield signal (δ 11.3) is observed, thus indicating the presence of only **11a**, in agreement with results for **5** (Figure 1c).

Attempted hydrolysis of **6** (24 hours in refluxing potassium hydroxide-ethanol-water solution) was unsuccessful; starting material was recovered.

Thus, the appropriate alkanoyl isoquinoline Reissert compounds afford convenient synthetic routes to novel benzopyrrocoline derivatives.

EXPERIMENTAL

General.

Melting points are corrected. Infrared spectra were recorded on a Perkin Elmer Model 237 and on a Beckman Model IR4, uv spectra on a Cary Model 15 and ^{1}H nmr spectra on Varian A60 and Jeolco C60H instruments utilizing tetramethylsilane as an internal standard.

Direct Synthesis of Benzopyrrocoline Derivatives.

The synthesis of **6** is representative. To a solution of 2.12 g (0.0100 mole) of 2-acetyl-3-methyl-1,2-dihydroisoquinaldonitrile (**1**), R = R_1 = CH_3) [3] and 4.0 ml (0.0400 mole) of isopropyl iodide in 30 ml of dry dimethylformamide (DMF) was added 0.50 g (0.010 mole) of 50% sodium hydride in mineral oil. The mixture was stirred for 1 hour, poured onto ice and filtered to afford 2.15 g (85%) of yellow solid. Recrystallization from ethanol gave colorless needles, mp 274.0-275.0°.

Indirect Synthesis of Benzopyrrocoline Derivatives.

The synthesis of **5** is representative. To a solution of 1.25 g (5.19 mmoles) of 1-isopropyl-2-acetyl-1,2-dihydroisoquinaldonitriel (**2a**) [3] in 20 ml of dry DMF was added 0.25 g (5.2 mmoles) of 50% sodium hydride/mineral oil dispersion. The mixture was stirred for ¾ hour, poured onto ice and filtered to yield 0.90 g (72%) of crude **5**. Recrystallization from ethanol-water led to cream colored crystals, mp 251.5-252.5° dec.

Catalytic Reductions.

The procedure for reduction of **7** to **11** is typical. A mixture of 1.00 g, (3.94 mmoles) of **7**, 0.1 g 10% palladium-on-carbon, 4 drops of concentrated hydrochloric acid and 100 ml of ethanol was shaken under 60 psig hydrogen pressure for 2 hours, during which time 5.2 mmoles of hydrogen was absorbed. The mixture was filtered and taken to dryness *in vacuo*. The residue was taken up in chloroform, washed with 1% sodium hydroxide and water, dried (sodium sulfate) and taken to dryness, leaving 0.90 g (89%) of nearly colorless solid, mp 145-155°. Recrystallization from ethyl acetate-hexane yielded colorless plates, mp 212.3-215.0°.

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