Transformations of Some Substituted Methylene Heterocycles with Some Nucleophiles (1)

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To the ring nitrogen substituted *o*-methylene derivatives of pyridine, pyridazine, quinoline and isoquinoline were transformed into the corresponding pyrazolyl derivatives when treated with hydrazine hydrate. On the other hand, the substituted methylene derivatives of quinoline or isoquinoline were transformed with aqueous sodium hydroxide or with sodium ethylate into 2-methylquinoline or 1-methylisoquinoline. This reaction represents a facile introduction of a methyl group in the above mentioned heterocycles.

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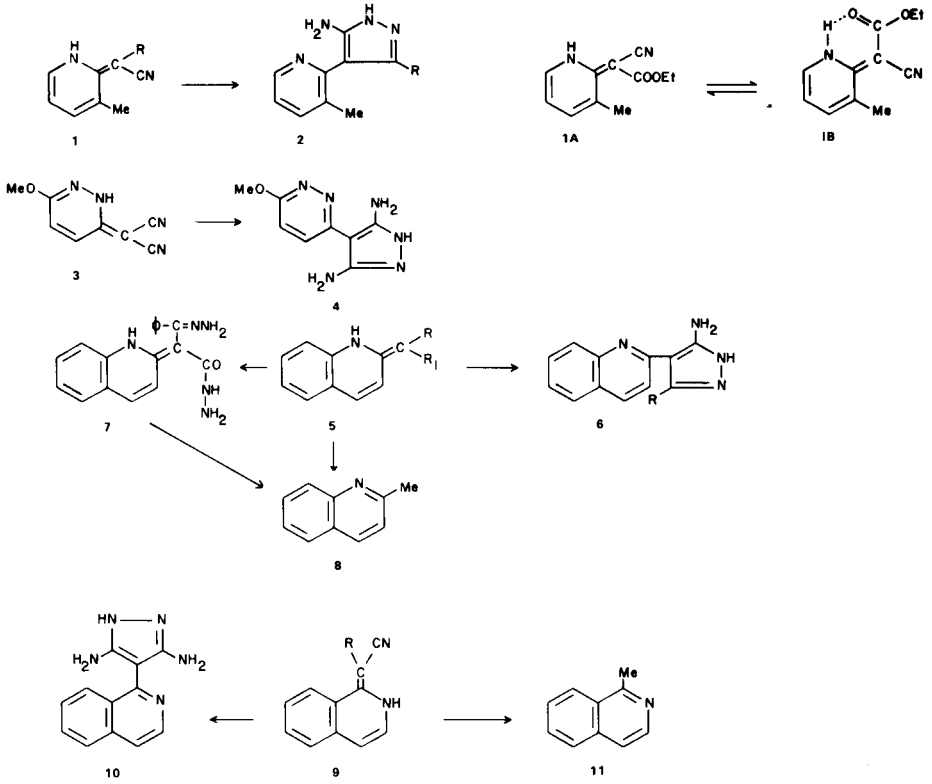
As a part of our investigation on heterocyclic *N*-oxides (2-8) we have recently reported on the reactions of some halogenated heterocycles and heterocyclic *N*-oxides with compounds containing reactive methylene groups (9). Reactions of heterocyclic *N*-oxides with nucleophilic carbon compounds in the presence of an acylating agent are rationalized as nucleophilic reactions of initially formed *O*-acyl heterocycles which afford the α- or γ-substituted products, the reaction being accompanied by deoxygenation of the *N*-oxide function (9-12).



Although this reaction permits the introduction of a substituted methylene group into various heterocycles (8,9), we could observe several cases of failure. Thus, the reaction between isoquinoline *N*-oxide and ethyl benzoylacetate or ethyl acetoacetate in the presence of acetic anhydride yielded 1(2*H*)isoquinolone even at 40°. It appears, that the attack of the acetate is preferential to that of the employed keto esters, although with other carbon nucleophiles, such as malononitrile or ethyl cyanoacetate the reaction took place (9). In addition, we could establish that contrary to earlier reports according to which isoquinoline *N*-oxide is converted into 1(2*H*)isoquinolone in boiling acetic anhydride after several hours (13,14), this transformation takes place already at 40°. Under these conditions, the cyclic lactam is formed in about 60% yield after 24 hours. In a similar manner, 3-methylpyridine 1-oxide is transformed in the presence of ethyl benzoylacetate and acetic anhydride into 3-methyl-2(1*H*)pyridone. On the other hand, a similar reaction in the pyridine series with malononitrile or ethyl cyanoacetate afforded the corresponding substituted methylene derivatives **1** (R = CN or COOEt), although in low yield. The nmr spectrum of the carbethoxy compound (**1**, R = COOEt) revealed that in chloroform solution two forms are present and the preponderant one is that with the cis-orientation of the carbethoxy group with regard to the ring nitrogen. This is understandable, if we take into consideration that this arrangement enables the formation of a hydrogen bonded species (**1B**) (9).

Recently, we have also shown (9) that substituted methylene heterocycles are convenient sources for the preparation of carboxyheterocycles which are otherwise difficultly accessible by other conventional methods.

As continuation of our interest in the chemistry of substituted methylene heterocycles, we have investigated their behaviour towards some nucleophiles. Heterocycles with a dicyanomethylene group reacted with hydrazine hydrate to afford at position 4 substituted 3,5-diaminopyrazoles as **4**, **10** and **2** or **6** (R = NH_2). With the related cyanocarbethoxymethylene compounds the corresponding amino-hydroxy derivatives (**2** or **6**, R = OH) (15) were obtained. Contrary to these cyclizations the carbethoxy benzoyl analog **5** (R = PhCO, R_1 = COOEt) did not form a pyrazole but instead a stable hydrazide-hydrazone **7** was obtained.

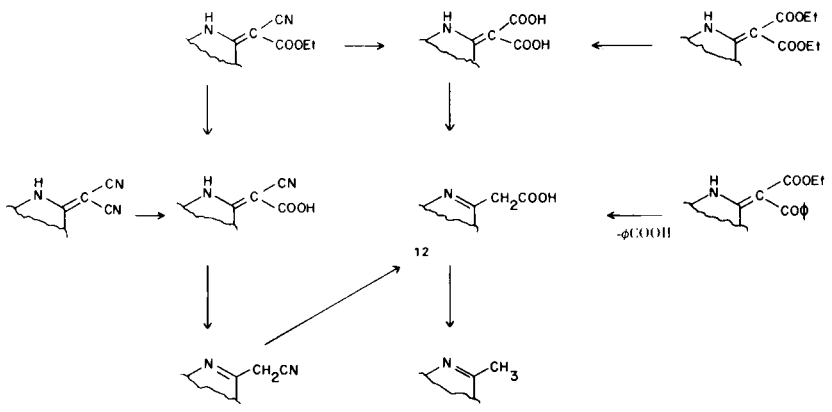
A completely different transformation took place in the presence of either sodium ethylate or aqueous sodium hydroxide. In all these cases, irrespective of the substituents at the methylene group, the side chain was transformed into a methyl group. Even the hydrazide-hydrazone **7** gave 2-methylquinoline under such reaction conditions. The transformation could be equally well applied to the corresponding isoquinolines, but failed with the monocyclic azines. It is anticipated that this transformation involves the formation of an intermediate heteroaryl substituted acetic acid (**12**) which is readily decarboxylated to give the corresponding methyl derivative (Scheme 1). In this manner, in a relatively simple manner a methyl group in α-position to the ring nitrogen of quinolines or isoquinolines can be introduced and the yields were fairly good. A method for direct introduction of a methyl group using methylsulfinyl carbanion has been described (17), however the methyl group is introduced into the quinoline ring at position 4. Other, less common methods for introducing a methyl group directly into the heterocyclic nucleus involve transformations with organo-metallic compounds (18) and 2-methylquinoline has been prepared also by the reaction with the Wittig reagent (19).

EXPERIMENTAL (20)

2(1*H*)Dicyanomethylene-3-methylpyridine (1, R = CN).

A solution of 3-methylpyridine 1-oxide (1.09 g.) in acetic

Scheme 1



anhydride (3 ml.) was treated portionwise under stirring with malononitrile (0.66 g.). At room temperature an intense red colour developed and the reaction mixture was heated at 40-50° for 4 hours. Upon standing on ice overnight, the separated brownish crystals were filtered off and crystallized from ethanol and *N,N*-dimethylformamide (yield 42 mg., 3%), m.p. 220-225°; mass spectrum: M^+ = 157; nmr (DMSO-d_6): τ = 2.42 (dd, H_4), 3.0 (dd, H_5), 2.25 (dd, H_6), 7.78 (s, Me), 5.0 (broad, NH), $J_{4,5}$ = 8.0, $J_{5,6}$ = 4.0 Hz.

Anal. Calcd. for $C_9H_7N_3$: C, 68.77; H, 4.49; N, 26.74. Found: C, 68.99; H, 4.90; N, 26.52.

2(1*H*)Cyanocarbethoxymethylene-3-methylpyridine (**1**, R = COOEt).

The compound was prepared in a similar manner as above from ethyl cyanoacetate after 7 hours at 40° in 24% yield, m.p. 185°; mass spectrum: M^+ = 204; nmr: Form A (deuteriochloroform): τ = 2.5 (m, H_4, H_6), 3.05 (H_5, m), 7.60 (s, 3-Me), 5.90 (q, CH_2Me), 8.50 (t, CH_2CH_3), J_{Et} = 7.2 Hz. Form B (deuteriochloroform): τ = 2.25-3.15 (m, H_4, H_5, H_6), 7.75 (s, 3-Me), 5.80 (q, CH_2Me), 8.60 (t, CH_2CH_3), J_{Et} = 7.2 Hz.

Anal. Calcd. for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.49; H, 6.10; N, 14.17.

2(3′,5′-Diaminopyrazolyl-4′)-3-methylpyridine (**2**, R = NH_2).

A mixture of the dicyanomethylene compound **1** (R = CN) (157 mg.), ethanol (4 ml.) and hydrazine hydrate (0.5 g. of 80%) was heated under reflux for 6 hours. Upon cooling, the separated crystals were filtered off and crystallized from ethanol (yield 35 mg., 19%), m.p. 245°; mass spectrum: M^+ = 189; nmr (DMSO-d_6): τ = 2.5 (m, H_4, H_5), 1.67 (m, H_6), 7.75 (s, 3-Me), 4.6 (broad, NH_2).

Anal. Calcd. for $C_9H_{11}N_5$: C, 57.12; H, 5.86; N, 37.02. Found: C, 57.02; H, 5.95; N, 36.87.

In a similar manner the following were prepared:

2(3′-Hydroxy-5′-aminopyrazolyl-4′)-3-methylpyridine (**2**, R = OH).

This compound was prepared from **1** (R = COOEt) after 30 hours, m.p. 300-305°; mass spectrum: M^+ = 190; nmr (DMSO-d_6): τ = 1.90 (d, H_4, partial overlap with H_6), 2.60 (dd, H_5), 1.8 (d, H_6, partial overlap with H_4), 7.84 (s, 3-Me), $J_{4,5}$ = 8.5, $J_{5,6}$ = 3.0 Hz.

Anal. Calcd. for $C_9H_{10}N_4O$: C, 56.83; H, 5.30; N, 20.46. Found: C, 56.88; H, 5.65; N, 20.80.

3-(3′,5′-Diaminopyrazolyl-4′)-6-methoxypyridazine (**4**).

Compound **4** was obtained from **3** (9) after 2 hours in 25% yield, m.p. 259-260°; mass spectrum: M^+ = 206; nmr (DMSO-d_6): τ = 2.22 (d, H_4), 2.96 (d, H_5), 6.03 (s, OMe), 4.65 (broad, NH), $J_{4,5}$ = 9.5 Hz.

Anal. Calcd. for $C_8H_{10}N_6O$: C, 46.59; H, 4.89; N, 40.76. Found: C, 47.02; H, 5.20; N, 40.52.

2(3′,5′-Diaminopyrazolyl-4′)-quinoline (**6**, R = NH_2).

This compound was prepared from **5** (R = R_1 = CN) (9) after 2 hours in 75% yield, m.p. 306-310°; mass spectrum: M^+ = 225; nmr (DMSO-d_6): τ = 2.20 (d, H_3), 1.90 (d, H_4), 2.4 (m, $H_{5,6,7,8}$) $J_{3,4}$ = 8.5 Hz.

Anal. Calcd. for $C_{12}H_{11}N_5$: C, 63.98; H, 4.92; N, 31.09. Found: C, 64.00; H, 5.19; N, 31.33.

2-(3′-Hydroxy-5′-aminopyrazolyl-4′)quinoline (**6**, R = OH).

Compound **6** was obtained from **5** (R = CN, R_1 = COOEt) (21) after 30 hours in 8% yield, m.p. 280-285°; mass spectrum: M^+ = 226.

Anal. Calcd. for $C_{12}H_{10}N_4O$: C, 63.70; H, 4.46; N, 24.77. Found: C, 63.48; H, 4.43; N, 25.09.

1(3′,5′-Diaminopyrazolyl-4′)isoquinoline (**10**).

This compound was prepared from **9** (R = CN) (9) after 24 hours in 62% yield, m.p. 256-258°; mass spectrum: M^+ = 225.

Anal. Calcd. for $C_{12}H_{11}N_5$: C, 63.98; H, 4.92; N, 31.09, Found: C, 64.04; H, 5.20; N, 30.97.

Hydrazone of 2(1*H*)Hydrazinocarbonyl Benzoylmethylenequinoline (**7**).

A solution of **5** (R = COPh, R_1 = COOEt) (9) (0.319 g.) in ethanol (3 ml.) was treated with hydrazine hydrate (0.5 ml. of 80%) and the reaction mixture was heated under reflux for 3 hours. Upon cooling, the product which separated was filtered off and crystallized from ethanol (yield 0.25 g., 79%), m.p. 183-185°; mass spectrum: M^+ = 319.

Anal. Calcd. for $C_{18}H_{17}N_5O$: C, 67.69; H, 5.37; N, 21.93. Found: C, 67.58; H, 5.49; N, 21.67.

Formation of 2-Methylquinoline (**8**).

a) A mixture of the dicyanomethylene compound **5** (R = R_1 = CN) (9) (193 mg.) and aqueous sodium hydroxide (3 ml. of 2*N*) was heated in an autoclave at 150-160° for 5 hours. The reaction mixture was filtered, the filtrate neutralized and extracted with chloroform. The solvent was evaporated *in vacuo*, the residue was identified as 2-methylquinoline (mass spectrum: M^+ = 143) and isolated as the picrate (yield 80%), m.p. 193-195° (lit. (22) gives m.p. 191°).

Similarly, the cyanocarbethoxymethylene compound **5** (R = CN, R_1 = COOEt) (21) was converted to **8** when heated with 2*N* sodium hydroxide under reflux for 5 hours and isolated as the picrate (yield 74%).

b) The benzoylcarbethoxymethylene derivative **5** (R = COPh, R_1 = COOEt) (9), when heated under reflux with an alcoholic solution of sodium ethylate for 5 hours, afforded after neutralization and extraction with chloroform pure 2-methylquinoline, isolated as the picrate, in 87% yield. Alternatively, 2*N* sodium hydroxide can be employed and after 4 hours under reflux and after neutralization benzoic acid was filtered off and the residue was extracted with chloroform to give compound **8**.

c) The hydrazide-hydrazone **7** and 2*N* sodium hydroxide were heated under reflux for 5 hours. The reaction mixture was neutralized, benzoic acid was filtered off and the remaining solution was extracted with chloroform to give 2-methylquinoline, isolated as the picrate, in 66% yield.

Formation of 1-Methylisoquinoline (**11**).

A mixture of 1(2*H*)dicyanomethyleneisoquinoline (**9**, R = CN) (9) (193 mg.) and aqueous sodium hydroxide (3 ml. of 2*N*) was heated in an autoclave at 150° for 5 hours. The reaction mixture was filtered, the filtrate was neutralized and extracted with chloroform. The solvent was evaporated to dryness, the residue was isolated and identified as the picrate of 1-methylisoquinoline in 58% yield, m.p. 211-213° (lit. (23) gives m.p. 206-208°).

1-Methylisoquinoline was also obtained from **9** (R = COOEt) (9) after treatment with aqueous sodium hydroxide under reflux for 5 hours. It was isolated as the picrate in 69% yield.

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