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REACTION OF CYTISINE WITH FORMALIN

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The reaction of cytisine with formalin in various solvents was studied. Methylene-bis-cytisine was produced in addition to the expected N-methylolcytisine in all solvents except acetone, in which N-(3-oxobutyl)cytisine was produced.

Key words: cytisine, formalin, *bis*-cytisinomethane, *N*-(3-oxobutyl)cytisine.

The combination of various natural fragments in a single molecule is interesting regarding their mutual effect on the biological activity of the resulting compounds. In this regard, *N*-methylolcytisine (**1**) might be an interesting synthon [1].

The preparation of **1** by reaction of cytisine (**2**) with formalin (35%) in ether and the formation of *bis*-cytisinomethane (**3**) by the reaction in absolute alcohol with added $Ca(OH)_2$ have been reported [1].

The use of ether as the solvent for production of **1** was impractical because of the poor solubility of cytisine in it. Therefore, we compared the reaction of cytisine with formalin (30%) in various solvents (ether, methanol, ethanol, hexane, chloroform, water, dioxane, acetone).

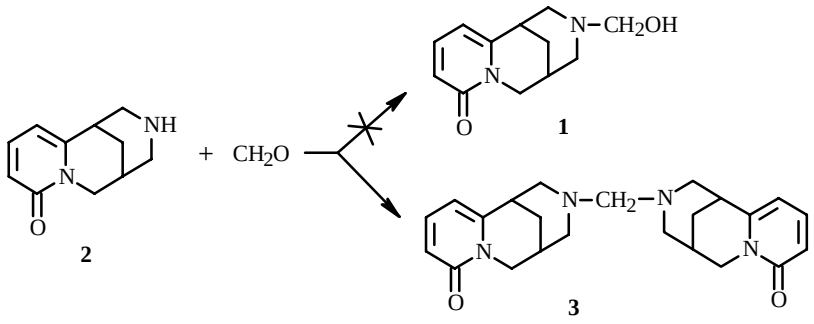
The reaction mixture of cytisine and formalin in the appropriate solvents was held at room temperature for 4-6 h. Chromatographic monitoring showed that a certain amount of unreacted cytisine remained in all reactions regardless of the solvent and that a product with R_f 0.7 was formed.

The reaction in ether produced crystals of **3a**, mp 131-132°C; in acetone, 115°C (**4**), in other solvents, 213-215°C (**3**). The mass spectrum of the last had peaks for a molecular ion with *m*/*z* 392 and for ions with *m*/*z* 204, 203, 190, 160, 159, 147, and 146, which confirmed the structure of **3** as *bis*-cytisinomethane.

According to the literature [1], it can be hypothesized that *N*-methylolcytisine forms in ether, for which mp 110-114°C was reported [1].

The IR spectrum of **3a** obtained from the reaction in ether contained a broad absorption band for active H with a maximum at 3490 cm^{-1}. However, the melting point of **3a** was higher than that found for **1**. The PMR spectrum showed that **3a** and **3** had the same spectrum. An x-ray structure analysis proved that **3a** was a crystal hydrate of **3** [2].

Thus, all attempts to prepare **1** were inconclusive, probably due to the high reactivity of **1**, which led to its further reaction with cytisine and formation of the *bis*-product **3**, which was not only the synthetic product but also a natural compound (12,12′-methylenedicytisine) that was isolated from *Maackia amurensis* [3].



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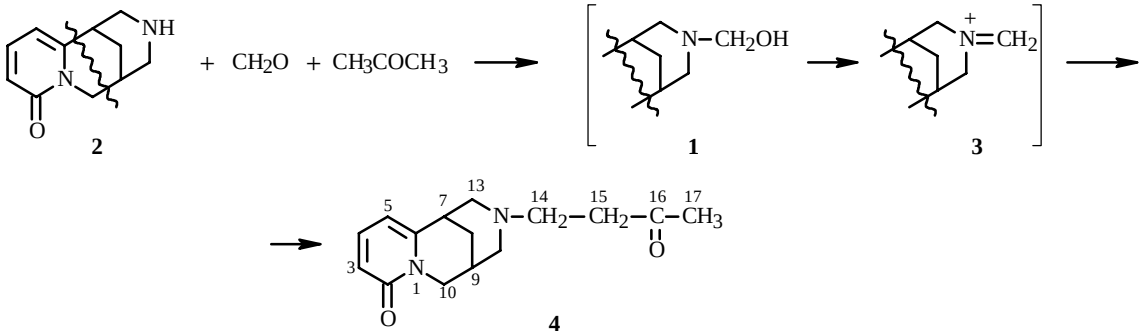
Even more interesting results were obtained on performing the reaction in acetone, where the solvent was involved in the reaction and gave **4** in 87% yield. The IR spectrum of **4** exhibited absorption bands for *trans*-quinolizidine at 2700-2800 cm^{-1}, α-pyridone at 1651, and a ketone at 1706. The mass spectrum of **4** had a peak for a molecular ion with *m*/*z* 260 and peaks for ions with *m*/*z* 218, 204, 203, 190, 160, and 146, corresponding to a cytisine derivative with a substituent on the N atom with a mass of 71 amu.

Detailed analysis of the HSQC, COSY, and HMBC spectra of **4** enabled signals to be assigned to specific C and H atoms.

The PMR spectrum of **4** showed signals for all protons of cytisine. However, the signal for the C-9 proton appeared at weaker field at δ 2.393 ppm (in cytisine, at δ 2.18 ppm) together with a $CO–CH_2$ group as a 3H multiplet.

A singlet of a C-methyl at δ 1.851 and a triplet of a $N–CH_2$ at δ 2.445 ppm were observed in the spectrum of **4** in addition to signals from protons of the cytisine skeleton.

The results for **4** proved that the structure was *N*-(3-oxobutyl)cytisine, which was probably formed through a Mannich reaction [4, 5].



N-(3-oxobutyl)cytisine was synthesized previously from cytisine and methylvinylketone with heating (60°C) for 3 h to prove the structure of **4** isolated from *M. amurensis* [6].

Our method for preparing **4** can be recommended as a preparative method for synthesizing *N*-(3-oxobutyl)cytisine because it is simpler and gives a pure product in high yield.

EXPERIMENTAL

General Comments. Column chromatography used KSK silica gel; TLC, the same silica gel and $CHCl_3$:CH_3OH (4:1) with development by I_2 and Dragendorff's solution.

NMR spectra of *N*-(3-oxobutyl)cytisine were recorded on a Bruker WM-250 spectrometer at working frequency 250 MHz for protons and 62.9 MHz for ^{13}C atoms in DMSO-d_6; IR spectra, on a Perkin—Elmer 2000 instrument (KBr disks); PMR spectra of *bis*-cytisinomethane, on a Tesla spectrometer at working frequency 100 MHz in $CDCl_3$.

***bis*-Cytisinomethane (3)** (12,12′-methylenedicytisine). A solution of cytisine (0.5 g) in various solvents (alcohol, methanol, hexane, chloroform, dioxane, water, 5 mL) was treated with formalin (0.25 mL, 30%). The mixture was held at room temperature for 4-6 h. Solvent was distilled. The reaction mixture was separated over a SiO_2 column to afford *bis*-cytisinomethane (**3**, 0.3 g, from water), yield 70%, mp 210-215°C, $C_{23}H_{28}N_4O_2$, R_f 0.7.

IR spectrum (ν, cm^{-1}): 3490, 3455, 2945, 2820, 1651 (N–C=O), 1547 (C=C), 1163, 1145.

Mass spectrum (*m*/*z*, I_{rel}, %): 392 (6.1) $[M]^+$, 204 (29.7), 203 (87.7), 191 (13.7), 190 (74.8), 172 (3.8), 163 (4.5), 162 (12.9), 161 (19.8), 160 (68.7), 159 (84.7), 149 (14.5), 148 (58.7), 147 (91.6), 146 (100), 135 (12.9), 134 (54.1), 131 (60.3), 121 (16.8), 118 (25.2), 117 (38.9), 109 (51.9), 96 (6.1), 95 (8.4), 94 (22.9), 93 (38.1), 82 (9.1), 81 (51.1), 76 (47.3), 71 (4.5), 70 (17.5), 68 (31.3), 65 (44.2), 59 (13.7), 58 (17.5), 57 (19.0), 55 (21.3), 53 (22.9), 51 (25.9), 45 (9.1), 44 (22.1), 43 (30.5).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 1.74 (2H, m, H-8, H-8′), 1.88 (2H, m, H-8, H-8′), 2.13 (2H, br.s, H-9, H-9′), 2.24 (4H, m, H-13), 2.8-2.50 (6H, H-7, H-11), 2.64 (2H, s, $N–CH_2–N$), 3.73 (2H, dd, J = 15.4, 7, H-10, H-10′), 3.98 (2H, d, J = 15.4, H-10, H-10′), 5.58 (2H, dd, J = 7, 1.2, H-5, H-5′), 6.37 (2H, dd, J = 9, 1.2, H-3, H-3′), 7.17 (2H, dd, J = 9, 7, H-4, H-4′).

12,12′-Methylenedicytisine Monohydrate (3a). A mixture of cytisine (0.16 g, 0.84 mmol), ether (50 mL), and formalin (30%, 0.08 mL, 0.84 mmol) was held for 4 h at room temperature. Solvent was partially distilled. The resulting crystals were separated to afford **3a** (0.17 g), mp 131-132°C [2].

***N*-(3-Oxobutyl)cytisine (4).** A solution of cytisine (5 g, 0.026 mol) in acetone (30 mL) was treated with formalin (30%, 2.5 mL, 0.026 mol). The mixture was held at room temperature for 6 h. The resulting precipitate was filtered off to afford **4** (3.3 g). Solvent was distilled. The solid was separated over a column of silica gel with elution by $CHCl_3$ and $CHCl_3$:CH_3OH to afford an additional amount of **4** (2.67 g), yield 87%, $C_{15}H_{21}N_2O_2$, mp 113-115°C, R_f 0.7.

IR spectrum (ν, cm^{-1}): 2966, 2939, 2827, 2794 (*trans*-quinolizidine), 1706 (C=O), 1651 (N–C=O), 1569, 1547 (C=C).

Mass spectrum (*m*/*z*, I_{rel}, %): 261 (3.47) $[M]^+$, 260 (17.3), 218 (55.5), 204 (11.8), 203 (34.0), 191 (7.6), 190 (35.4), 174 (3.4), 163 (4.8), 162 (9.0), 161 (10.4), 160 (27.7), 152 (5.5), 149 (12.5), 148 (29.1), 146 (100), 135 (6.9), 134 (26.3), 123 (3.4), 122 (9.7), 118 (13.1), 117 (20.8), 115 (27.0), 114 (61.8), 109 (22.9), 104 (11.1), 98 (3.4), 96 (5.5), 94 (10.4), 93 (12.5), 83 (3.4), 82 (23.6), 72 (20.8), 71 (38.8), 59 (9.0), 57 (11.1), 56 (15.2), 55 (37.5), 45 (5.5), 44 (7.6), 43 (22.2), 42 (26.3).

PMR spectrum (DMSO-d_6, δ, ppm, J/Hz): 1.67 (1H, dt, J = 2.6, 13, H-8), 1.78 (1H, dt, J = 2.6, 13, H-8), 1.85 (3H, s, CH_3-17), 2.17 (1H, d, J = 2.1, H-11), 2.25 (1H, d, J = 2.1, H-13), 2.38-2.43 (5H, m, H-9, CH_2-15, CH_2-14), 2.79 (1H, d, J = 2.1, H-13), 2.87 (1H, d, J = 2.1, H-11), 3.00 (1H, br.s, H-7), 3.67 (1H, dd, J = 15.4, 6.7, H_a-10), 3.71 (1H, d, J = 15.4, H_e-10), 6.05 (1H, d, J = 9, H-5), 6.18 (1H, d, J = 7, H-3), 7.30 (1H, dd, J = 9, 7, H-4).

^{13}C NMR spectrum (DMSO-d_6, 62.9 MHz): 162.80 (C-2), 115.13 (C-3), 138.56 (C-4), 103.52 (C-5), 151.5 (C-6), 34.43 (C-7), 25.05 (C-8), 27.15 (C-9), 49.40 (C-10), 59.14 (C-11), 60.02 (C-13), 52.07 (C-14), 40.49 (C-15), 29.26 (C-17).

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