3-O-(1-PHENYLTETRAZOL-5-YL)MORPHINE IN THE ACID-CATALYZED MORPHINE-APOMORPHINE REARRANGEMENT: FORMATION OF A SIDE PRODUCT DUE TO 1-PHENYLTETRAZOLE GROUP MIGRATION

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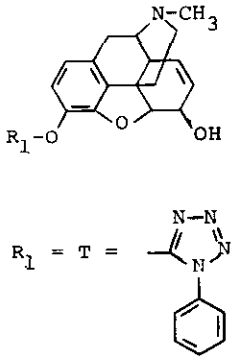
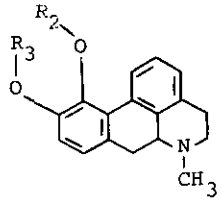
Abstract - Acid catalyzed rearrangement of the title compound leads to a second aporphine derivative in addition to the expected product, 10-O-(1-phenyltetrazol-5-yl)-apomorphine. This side product is isomeric with the expected product, and it was shown to be 11-O-(1-phenyltetrazol-5-yl)apomorphine, apparently formed by tetrazole ring migration in the course of the acid catalyzed rearrangement of the morphine derivative.

In the course of synthetic studies leading to aporphine ring derivatives[1] the 3-O-(1-phenyltetrazol-5-yl) ether **1** of morphine was subjected to acid-catalyzed rearrangement with methanesulfonic acid, according to a literature procedure[2]. These workers reported isolation of a single product from this reaction, the 10-O-(1-phenyltetrazol-5-yl) ether **2** of apomorphine.



1 R_1 = T =



2 R_2 = H; R_3 = T

3 R_2 = T; R_3 = H

4 R_2 = CH_3; R_3 = T

5 R_2 = T; R_3 = CH_3

6 R_2 = H; R_3 = CH_3

7 R_2 = H; R_3 = H

8 R_2 = CH_2Ph; R_3 = T

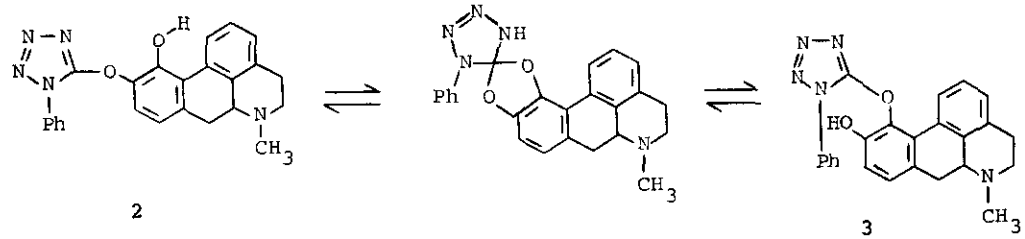
In the present work, thin layer chromatographic analysis of the product of the rearrangement, using a large number of solvent systems, indicated that the product was homogenenous. However, 360 MHz proton nmr spectra strongly suggested that the product was not a single chemical entity. All attempts to separate the components of this material by recrystallization and/or chromatographic techniques failed. However, conversion of the product to its methyl ether(s) with diazomethane afforded material which could be separated chromatographically[1]: the major component was the expected product, the 11-methyl ether **4** of 10-O-(1-phenyltetrazol-5-yl)apomorphine, and the minor component was speculated to be the ether positional isomer,

the 10-methyl-11-(1-phenyltetrazol-5-yl) ether **5**. Nmr spectra of the two products revealed significant differences: the O-methyl protons of **4** appeared at δ 3.50 and the same protons of **5** appeared downfield at δ 3.80. These relative positions are rationalized on the basis that the methyl group on the 11-oxygen of **4** undergoes non-bonded interactions with the bulky substituent at position 10 and with the hydrogen at position 1 of the aporphine ring system, and as a consequence, the 11-O-methyl of **4** is oriented out of the plane of the ring, and is thus shielded[3]. Mass spectra of the two methyl ether products, **4** and **5**, were similar (M^+ = 425). The structure of **5** was confirmed by conversion of an authentic sample of apocodeine (**6**)[4] into its 1-phenyltetrazol-5-yl ether. Spectral (ir, ms, nmr) and chromatographic properties of this synthesized product were identical with those of the methyl ether derivative **5**[5] of the acid-catalyzed rearrangement side product.

Renewed efforts to obtain the putative phenolic products **2** and **3** of the acid-catalyzed rearrangement in pure form resulted in chromatographic isolation of material, the mass spectrum of which showed a molecular ion of 411, consistent with either **2** or **3**. Proton nmr spectra displayed two different acidic proton resonances (at δ 9.98 and 10.16). Attempts to recrystallize this product yielded material, the nmr spectrum of which, was more complex, the mass spectrum showed a molecular ion of 411, consistent with a mono-1-(phenyltetrazol-5-yl) ether of apomorphine **7**. It was concluded that this material was a mixture of the 10- and 11-mono ethers of apomorphine. This was substantiated by treatment with diazomethane, which produced a mixture of the isomeric monomethyl ethers **4** and **5**. These substances were separately subjected to the conditions employed for the acid-catalyzed rearrangement of the morphine derivative **1**. In the case of both **4** and **5**, the unchanged starting material was recovered, suggesting that any possible 1-phenyltetrazole ring migration on the aporphine ring system occurs only if the phenolic group adjacent to the 1-phenyltetrazole ether moiety is free.

Repeated attempts to cleave the methyl ether links of pure **4** and **5** yielded mixtures of the free phenols **2** and **3** in each instance. In a separate experiment, the pure *11-benzyl ether* **8**[6] *of* **2** *was subjected to catalytic* hydrogenolysis. This experiment also yielded a mixture of **2** and **3**.

The failure to obtain pure **2** or **3** may be rationalized on the basis of their propensity to interconvert via an intramolecular nucleophilic displacement involving a 5-membered transition state, as illustrated in Scheme 1.



Scheme 1. *Migration of (1-Phenyltetrazol-5-yl) Moiety in Apomorphine.*

These studies indicate that the 1-phenyltetrazol-5-yl moiety undergoes facile migration to an ortho-phenolic group under a variety of mild experimental conditions, and that this is likely an equilibrium process. Because of the wide use of this heterocyclic ether moiety in effecting reductive removal of phenolic oxygen from a ring system[7], it is necessary to recognize that the method may not be unequivocal in certain substrate molecules such as catechols.

ACKNOWLEDGEMENT

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REFERENCES AND NOTES

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5. The concentrated chromatography fraction, on standing in the cold room deposited an off-white powder, compound **5**: mp 148-150 °C; ir (KBr) 2940, 1595, 1575, 1535, 1500, 1450, 1286, 1250 cm^{-1}; ^1H nmr (60 MHz, $CDCl_3$) δ 8.00-6.86 (m, 10H), 3.80 (s, 3H), 3.33-2.16 (m, 7H), 2.56 (s, 4H); EIMS, m/z (rel intensity) 425 (M^+, 17), 280 (61), 264 (33), 249 (37), 236 (66), 220 (87), 208 (45), 194 (30), 178 (41), 165 (82), 152 (44), 117 (76), 91 (59), 77 (89), 65 (100). Anal. Calcd. for $C_{25}H_{23}N_5O_2$: C, 70.57; H, 5.45; N, 16.46. Found: C, 70.76; H, 5.70; N, 16.23.

6. Compound **8** recrystallized from methanol-water: mp 120-121 °C; ^1H nmr (360 MHz, $CDCl_3$) δ 8.18 (d, 1H, J = 7.7 Hz), 7.68-7.65 (m, 2H), 7.48-7.46 (m, 3H), 7.31 (d, 1H, J = 8.2 Hz), 7.24-7.10 (m, 6H), 6.94 (d, 2H, J = 6.6 Hz), 4.84 (d, 1H, J = 10.9 Hz), 4.47 (d, 1H, J = 10.9 Hz), 3.22-3.16 (m, 3H), 3.10-3.05 (m, 1H), 2.78 (bd, 1H, J = 13.6 Hz), 2.62-2.55 (m, 5H); EIMS, m/z (rel intensity) 501 (M^+, 8), 356 (16), 237 (10), 236 (14), 208 (18), 194 (11), 165 (17), 91 (100); Anal. Calcd. for $C_{31}H_{27}N_5O_2$: C, 74.21; H, 5.43; N, 13.97. Found: C, 73.95; H, 5.63; N, 13.60.

   Selective cleavage of the benzyl group in the presence of the tetrazolyl moiety was achieved using 5% Pd/C and H_2 in ethanol at ambient temperature for 24 h.

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