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Short Communication

Metaquat, a Paraquat Isomer Isolated from an Arrow Poison

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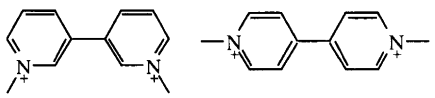
Compounds with a curare-like activity are characterized by their strong muscle relaxing effect. This kind of activity is most commonly caused by compounds having two quaternary nitrogen atoms or two tertiary nitrogen atoms[1,2] that become quaternary during metabolism.[3] The muscle relaxant effect is due to an interaction between the two quaternary nitrogen atoms and the acetylcholine receptors in the muscle.[1] Strychnine derivatives are compounds with a curare-like activity,[3] and it is very common that a strychnine derivative is the lethal component in South-east Asian arrow poisons.[4–7] When an animal is hit by an arrow poisoned with a compound with curare-like activity its heart stops immediately; the poison causes the heart-muscles to relax and the heart stops contracting. We have been able to identify a salt of the dication 1,1′-dimethyl-3,3′-bipyridinium, compound **1**, as the main component of an arrow poison used by the South-east Asian Orang Mentawai tribe,[8] whose description of the effect of their poison is similar to that of curare. Hence we expect that compound **1** has curare-like activity. A future study of the pharmacological activity of compound **1** will prove or disprove the curare-like activity of compound **1**; the results will be reported elsewhere.



1 **2**

Compound **1** is isomeric with the common herbicide Paraquat, 1,1′-dimethyl-4,4′-bipyridinium, compound **2**. However, compound **2** exhibited no curare-like activity when pure Paraquat dichloride was tested.[9] When 100 mg kg^{-1} Paraquat dichloride was injected into rats, death did not occur immediately;[10] hence Paraquat would not be an effective arrow poison: several grams of Paraquat dichloride would probably be needed to kill a 40 kg monkey. Shiau *et al.*[9] showed that commercially available Paraquat dichloride[11] has curare-like activity due to an unidentified impurity. A puzzling question arises; could Metaquat dichloride be the impurity in the commercially available Paraquat dichloride studied by Shiau *et al.*?

Experimental

The isolation of the salt of compound **1** was carried out as follows: 2 ml crude arrow poison sample were freeze-dried, and the residue (72 mg) was extracted with ethyl acetate, methanol and water in that order. The methanol fraction was purified by semi-preparative HPLC using an RP-18 column (diameter 10 mm, length 25 cm), methanol (3 ml min^{-1}) as the eluent and UV–VIS detector set at 264 nm and 294 nm. Five fractions were collected. Fraction 3 (6.8 mg) contained compound **1** and oleic acid in an 8:1 ratio based on ^{1}H NMR integrals.

The structure of the isolated salt was deduced from its 400 MHz ^{1}H and 63 MHz ^{13}C NMR spectra. Final proof of the identity of the isolated compound and compound **1** was provided by synthesis of 1,1′-dimethyl-3,3′-bipyridinium diiodide: 3,3′-bipyridyl[12] was reacted with methyl iodide (8 equiv.) in 2:25 dioxane–ethanol at 60 °C overnight, the precipitate was filtered off, washed with cooled ethanol and dried to give yellow crystals (m.p. 278–279 °C, (decomp.). Found C 32.51, H 3.01, N 6.00. Calc. for $C_{12}H_{14}I_2N_2$: C 32.75, H 3.21, N 6.37%) in 31% yield from 3,3′-bipyridyl. The ^{1}H NMR signals of the product, δ(DMSO-d_6): 9.70 (br s, 1 H), 9.16 (d, 1 H), 9.06, (d, 1 H), 8.40, (t, 1 H), 4.46, (s, 3 H), were identical with signals found in the ^{1}H NMR spectra (DMSO-d_6) of both fraction 3 and freeze-dried crude arrow poison. In the latter there were no other significant signals at a chemical shift above 3.8 ppm, indicating that

no other aromatic alkaloids (e.g. strychnine derivatives) were present in the arrow poison. The area below 3.8 ppm was dominated by the methylene protons of oleic acid. The ^{13}C NMR spectrum of fraction 3 and of the synthetic product, δ(DMSO-d_6): 146.1, 144.8, 143.3, 132.7, 127.9, 48.5, also agreed.

References and notes

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8. The inhabitants of Siberut, an island in the Mentawai archipelago 125 km west of Sumatra. The poison is produced by squeezing chilli leaves, bark and a root crop together in a small basket; the liquid obtained by this procedure is applied to the arrows with a small brush. The shaman of the Batmarak long house is gratefully acknowledged for supplying a sample of his arrow poison, but no plant samples or trivial plant names could be obtained due to linguistic difficulties.
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11. The commercially available Paraquat dichloride obtained by Shiau *et al.* was purchased from the herbicide company FEDA in Taiwan. It was produced by methylation of 4,4′-bipyridyl obtained by coupling of pyridine with sodium in anhydrous ammonia (Ref. 9).
12. This compound was synthesized as described by Tiecco, M., Testaferri, L., Tingoli, M., Chianelli, D. and Montanucci, M. *Synthesis 9* (1984) 736.

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