SYNTHESIS AND PROPERTIES OF TROPINONE ENAMINES

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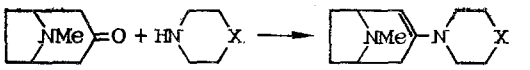
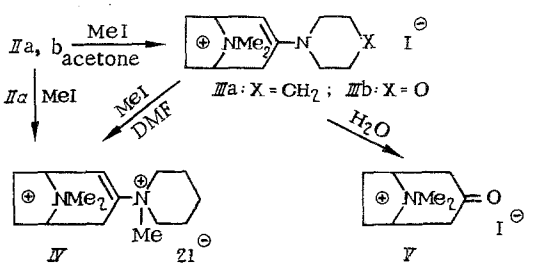
Investigations in recent years have shown that the conversion of ketones into enamines enables the latter to be used for new synthetic purposes for which the parent ketones could not be used [1]. There is therefore considerable interest in the development of synthetic routes to tropinone enamines, and in the study of the reactions of the latter with electrophilic reagents. Such a route would open up the possibility of using tropinone enamines for the preparation of disubstituted tropanes, of which the alkaloid cocaine is a particular example.

The only information on the synthesis of tropinone enamines is found in patents describing the preparation of 3-dimethylaminotropidine by treatment of tropinone (I) with tri-(NN-dimethylamino)arsine [2]. We have developed a general method for the preparation of tropinone enamines (IIa and b) by the reaction between I and cyclic secondary amines (piperidine and morpholine) in benzene solution in the presence of catalytic amounts of toluene-p-sulfonic acid and zeolite, the latter serving to adsorb the water which is formed in the reaction [3].



I — IIa: X = CH_2; IIb: X = O

The next step was an investigation of the reaction of the enamines (IIa and b) with electrophilic reagents. Since localization of electron density in these compounds occurs at the 'bridge' nitrogen and at the enamine grouping, it might be expected that the products would be dependent on the reaction conditions. In the event, treatment of acetone solutions of IIa and b with equimolar amounts of methyl iodide gave the methiodides (IIIa and b) in high yields, while reaction of IIa with an excess of methyl iodide in dimethylformamide resulted in reaction at both centers to form the bismethiodide (IV), which was also obtained by reaction of IIIa with methyl iodide.



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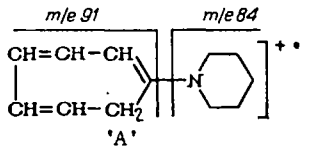
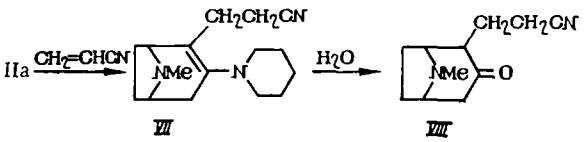
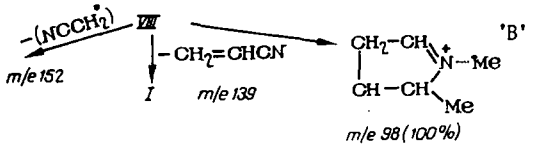
The structures of IIIa and b were confirmed by hydrolysis to tropinone methiodide (V) [4], and that of IV by mass spectral analysis. The mass spectrum of the latter compound showed a fragment with m/e 175, in agreement with structure 'A,' probably formed by dissociation of IV to IIa, followed by loss of methylamine. The proposed structure corresponds to the further fragmentation of the ion 'A' to form a hydrocarbon fragment with m/e 91, and a piperidine residue with m/e 84.



In order to exclude the possibility of attack by the electrophilic reagent at the 'bridge' and piperidine nitrogen atoms, the reaction of IIa with acrylonitril (VI) was examined. The reaction of IIa with VI proceeded with difficulty, forming a difficultly separable mixture of IIa and 2-(β-cyanoethyl)-3-(N-piperidino)tropidine (VII). The mixture was therefore hydrolyzed with water, and distilled to give 2-(β-cyanoethyl)-2-tropinone (VIII) (15%) and I (43%).



The structure of VIII was confirmed by its mass spectrum. The mol. wt. of the compound was 192, in agreement with structure VIII. Fragmentation of the molecular ion of VIII occurred as follows:



It is noteworthy that in the fragmentation of VIII by electron impact, the retroprocess is observed in which acrylonitrile is lost to form the molecular ion of I with m/e 139. The principal fragment observed in the mass spectrum of VIII corresponds in structure to 'B,' with m/e 98, which is typical of the fragmentation of compounds similar to VIII [5].

Of the compounds synthesized during this investigation, the bismethiodide (IV) was examined pharmacologically. The effects of IV on the peripheral m- and n-choline reactive systems were examined, together with its adrenolytic and antihistaminic activity. It was found that an initial dose of 0.5-1 mg/kg administered intravenously to cats stimulated respiration, raised the arterial pressure by 20-30 mm Hg, and shortened the nictatory membrane, i.e., it induced responses which are typical of substances which stimulate the vegetative ganglia. The mode of action of IV was investigated in experiments in which the vegetative ganglia were blocked by the intravenous administration of the ganglion-blocking agent temekhin, in a dose of 0.1 mg/kg. It was found that IV at a dose of 2 mg/kg, superimposed on the effects of the ganglion-blocking agent, did not give rise to the characteristic effects of ganglion stimulation, Thus, IV exerts a stimulant effect on the n-choline reactive system of the vegetative ganglia, but it is much less active in this respect than the known n-choline mimetic cytizine.

EXPERIMENTAL METHOD

IR spectra were recorded as pastes in vaseline oil on a Perkin-Elmer 457 spectrometer. UV spectra were recorded in alcohol solution on an EPS-3 recording spectrophotometer. The mass spectrum of IV was recorded on an LKB-9000 instrument at 70 eV, the compound being

heated to 200°. The mass spectrum of VIII was recorded on an MX-1303 instrument with an ionizing voltage of 30 eV.

3-(N-Piperidino)tropidine (IIa). A solution of 13.92 g (0.1 mole) of I, 12.77 g (0.15 mole) of piperidine, and 0.05 g of toluene-p-sulfonic acid in 50 ml of dry benzene was boiled for 45 h with 22.5 g (30 cm^3) of zeolite, previously dehydrated *in vacuo* (2mm, 300-320°, 3 h). The mixture was filtered, the zeolite washed with dry benzene, the solution evaporated *in vacuo*, and the residue distilled to give 8.33 g (40.4%) of IIa, bp 140-142° (9 mm), n_D^{20} 1.532. Found, %: C 75.66; H 10.76; N 13.60. $C_{13}H_{22}N_2$. Calc., %: C 75.68; H 10.75; N 13.57. IR spectrum: $\nu_{C=C}$ 1620 cm^{-1}. UV spectrum: λ_{max} 230 nm (log ε 3.8681), 333 nm (log ε 2.7404).

3-(N-Morpholino)tropidine (IIb). Synthesis as for IIa. Yield of IIb 8.18 g (39.3%), bp 141-143° (7 mm), n_D^{20} 1.533. Found %: C 69.52; H 9.63; N 13.32. $C_{12}H_{20}N_2O$. Calc., %: C 69.18; H 9.68; N 13.44. IR spectrum: $\nu_{C=C}$ 1628 cm^{-1}. UV spectrum: λ_{max} 228 nm (log ε 3.9175), 325 nm (log ε 2.3324).

Hydrolysis of IIb to Tropinone (I). A solution of 7.94 g (0.038 mole) of IIb in 15 ml of water was kept for 24 h at room temperature then saturated with potassium carbonate, extracted with chloroform, the chloroform removed, and the residue distilled to give I (4.47 g, 84.24%), bp 98-100° (12 mm), mp 40-41°.

3-(N-Piperidino)tropidine N_8-Methiodide (IIIa). To a solution of 13.1 g (0.065 mole) of freshly distilled IIa in 100 ml of dry acetone was added with cooling (0-3°) 5 ml (0.08 mole) of methyl iodide. The precipitate which separated on standing was filtered off, washed with acetone, and dried. Yield of IIIa, 18.53 g (81.86%), mp 119.5-120° (from isopropanol). Found, %: I 36.43; N 7.60. $C_{14}H_{25}IN_2$. Calc., %: I 36.44; N 8.04. IR spectrum: $\nu_{C=C}$ 1630 cm^{-1}.

3-N-(Morpholino)tropidine N_8-Methiodide (IIIb). Synthesized in a similar way to IIIa. Yield 86.8%, mp 147.5-148.5° (from absolute alcohol). Found%:C 44.60; H 6.52; I 36.2; N 7.81. $C_{13}H_{23}IN_2O$. Calc., %, C 44.58; H 6.62; I 36.23; N 8.00. IR spectrum: $\nu_{C=C}$ 1642 cm^{-1}.

Hydrolysis of IIa and IIIb, under conditions similar to those used for the hydrolysis of IIb to tropinone, gave tropinone methiodide (V), yield 68-76%, mp 258° (decomposition, from water), giving no depression of mp on admixture with a sample prepared by reaction of I with methyl iodide [4].

3-N-(Piperidino)tropidine N,N^1-Bismethiodide (IV). Method 1. A mixture of 16.24 g (0.079 mole) of freshly distilled IIa, 100 ml of dimethylformamide, and 15 ml (0.24 mole) of methyl iodide was heated at 85-90° for 9 h. The precipitate which separated (15.2 g) was filtered off, and a further 5 g of methyl iodide was added to the solution. After heating at 85-90° for a further 7 h the reaction mixture was evaporated to dryness *in vacuo*, and the residue combined with the abovementioned precipitate and dissolved in 35 ml of water. After keeping for 24 h at 20°, the precipitate of V which had separated (6.9 g, 32%) was filtered off and the aqueous solution evaporated to dryness *in vacuo*. The residue was triturated with acetone, filtered, and dried to give IV (14.64 g, 37.94%), mp 179-179.5° (from methanol). Found, %: C 36.85; H 5.83; I 51.68; N 5.37. $C_{15}H_{28}I_2N_2$. Calc., %: C 36.75; H 5.76; I 51.78; N 5.72. Method 2. A mixture of 2 g (0.0057 mole) of IIIa, 40 ml of dimethylformamide, and 2.5 ml (0.04 mole) of methyl iodide was heated at 95-100° for 5 h, the solution evaporated to dryness *in vacuo*, and the residue triturated with acetone, filtered, and dried. Yield of IV, 1.67 g (59.3%).

2-(β-Cyanoethyl)-3-tropinone (VIII). A solution of 13.31 g (0.0645 mole) of IIa and 4.45 g (0.084 mole) of freshly distilled VI in 50 ml of dry dioxane was boiled for 13 h, 4.45 g of VI added, and boiling continued for a further 7 h. Water (30 ml) was added to the reaction mixture, which was then heated on a boiling water bath for 3 h and evaporated to dryness *in vacuo*. The residue was dissolved in 40 ml of 2 N HCl, the solution decolorized with charcoal, basified with 25% aqueous ammonia to pH ∿ 9.0, and extracted with ether. The extract was evaporated and distilled. Fraction I consisted of I, yield 3.84 g (42.8%), bp 87-90° (7-8 mm), mp 40-41°. Fraction II was VIII, yield 1.88 g (15.2%), bp 168-170° (7-8 mm),

n_D^{20} 1.507. Found, %: C 68.99; H 8.49; N 14.31. $C_{11}H_{16}N_2O$. Calc., %: C 68.72; H 8.39; N 14.57. IR spectrum: $\nu_{C \equiv N}$ 2260, ν = O 1715 cm^{-1}. Picrate, mp 155.5-157° (from water). Found, %: N 16.50, $C_{17}H_{19}N_5O_8$. Calc. %: N 16.62.

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