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THE TOTAL SYNTHESIS OF WITHASOMNINE, A UNIQUE PYRAZOLE ALKALOID

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Withasomnine is a unique pyrazole alkaloid isolated from the roots of indian medicinal plants, Withania somnifera Dun.(Solanaceae) by Schröter et al.[1] and established the structure (IX), 4-phenyl-1,5-trimethylenepyrazole by using physical methods by the same authors.[1] Being interested in the chemical proof for the structure IX of withasomnine, we studied the total synthesis of IX.

The present communication relates to the total synthesis of the alkaloid.

In order to synthesize the alkaloid(IX), we took a route of the ring closure of the key intermediates, 4-phenyl-3-(3-halopropyl)-pyrazoles, prepared as follows.

Method A* : (Scheme 1)

4-Phenyl-3-hydroxymethylpyrazole(I), m.p.161-163^0, was chlorinated to the 3-chloromethyl compound(II) (HCl salt, m.p. 185-187.5^0), which was submitted to the Malonic ester synthesis using NaOEt as a base. As a result, three kinds of products III, IV and V were obtained, and the formation ratio of III to IV was inversely proportional to the amount of NaOEt used : III was a normal malonate, sticky needles, IR(film): 1730-1745cm^{-1}(C=O); IV was a new lactam ester, m.p. 123 -125^0, IR(Nujol): 1768cm^{-1}(lactam) and 1735cm^{-1}(ester), which could be enolizable and was separated out in the form of enolate salt(IV') from the reaction mixture ; and V was a symmetrical ester, m.p.192.5-194^0, IR(Nujol): 1735cm^{-1}(ester).

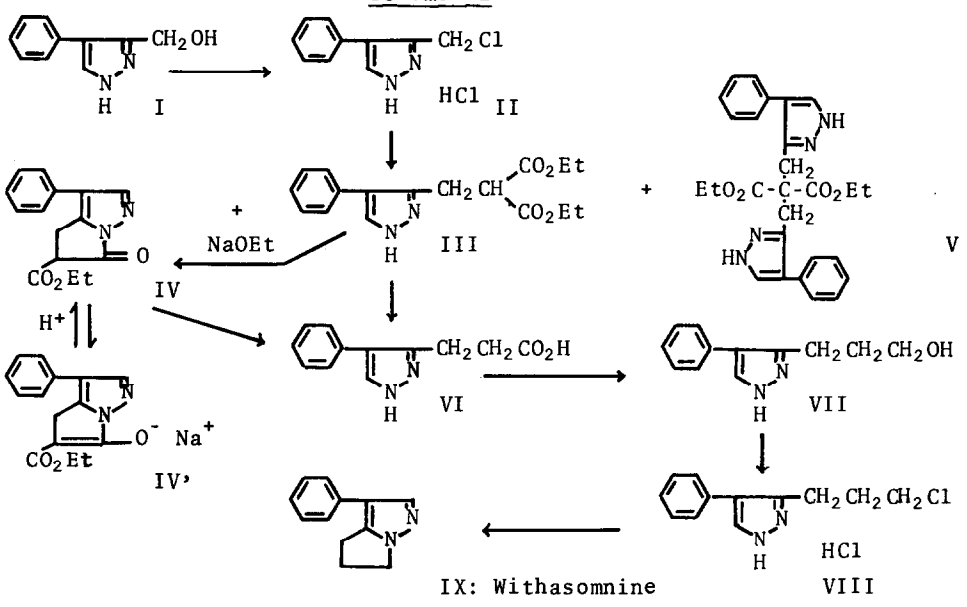
Since the treatment of the ester(III) with equimolecular NaOEt in EtOH at room temperature afforded the lactam ester(IV) in good yield, this transformation might have occurred in the reaction mixture in the presense of excess NaOEt.

By treatment with concd. HCl under reflux, III as well as IV was converted

into the same propionic acid(VI), m.p.144-146^0 which, by reduction with $LiAlH_4$, was converted into the corresponding propanol(VII), m.p.96-97.5^0.

4-Phenyl-3-(3-chloropropyl)-pyrazole(VIII), the required precursor of withasomnine, was prepared (as HCl salt, m.p.151.5^0) by chlorination of VII with thionyl chloride.

Scheme 1



The ring closure of the compound VIII to IX was accomplished by treating the former with bases such as NaOEt, KOH and triethylamine. The resulting 4-phenyl-1,5-trimethylenepyrazole(IX), m.p.117-118.5^0(m.p.117-118^0[1]), afforded the picrate, m.p.172-174.5^0(m.p.170-173^0[1]) and was identical in all physical properties (melting point, TLC, IR, NMR and Mass spectra) with those recorded for the natural withasomnine.[1]

From the above fact, we confirmed that withasomnine should be represented by the formula(IX), 4-phenyl-1,5-trimethylenepyrazole, as deduced by Schröter[1].

As one of the new derivatives of withasomnine, we obtained the methiodide , m.p.220-221^0, which was resistant to Hofmann Degradation.

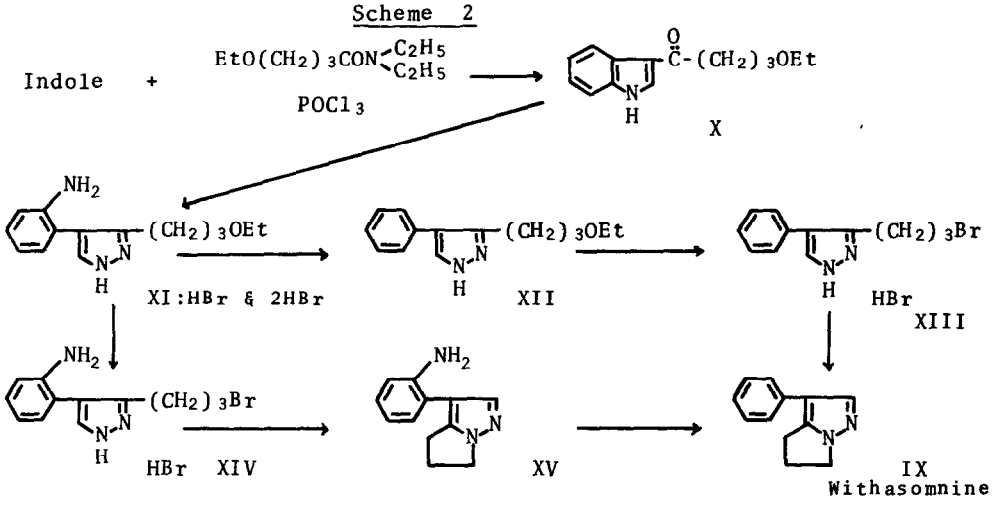
A more convenient synthetic method for withasomnine(IX) was also developed by us. (Method B : Scheme 2)

Method B* :

Under a condition similar to that reported by Anthony[2], we made acylation of indole into 3-(4-ethoxybutyroyl)-indole(X), m.p.138-141°, using $POCl_3$ and N,N-diethyl 4-ethoxybutyramide(b.p.100°/3mmHg).

In 1957, Alberti[3] achieved the transformation of 3-acylindoles to 4-(2'-aminophenyl)-pyrazoles by $NH_2NH_2 \cdot H_2O$. We have applied this procedure to the above indole(X) and obtained the required pyrazole(XI) in excellent yield.

Scheme 2



Thus obtained 3-(3-ethoxypropyl)-4-(2'-aminophenyl)pyrazole(XI), amber coloured viscous liquid, affords mono- and di-hydrochlorides(m.p.150-155° and 179-183°(decomp.) respectively). The final product (IX) can be obtained by the two different ways via the starting material(XI).

Firstly, 3-(3-ethoxypropyl)-4-phenylpyrazole(XII), m.p.34-36.5°, was prepared by reductive de-amination of the diazonium salt of XI by means of H_3PO_2. By treating XII with 47% HBr under reflux, 3-(3-bromopropyl)-4-phenylpyrazole(XIII) was obtained in the form of HBr salt, m.p.204-205°(decomp.).

The identical 4-phenyl-1,5-trimethylenepyrazole(IX) was obtained by completing the ring closure of XIII in the same manner as in the case of compound VIII in Method A.

Secondly, the direct bromination of XI was carried out by refluxing with 47% HBr to provide 3-(3-bromopropyl)-4-(2'-aminophenyl)pyrazole (HBr salt(XIV), m.p.168-181°(decomp.)). By treating XIV with base; e,g. KOH in hot ethanol an

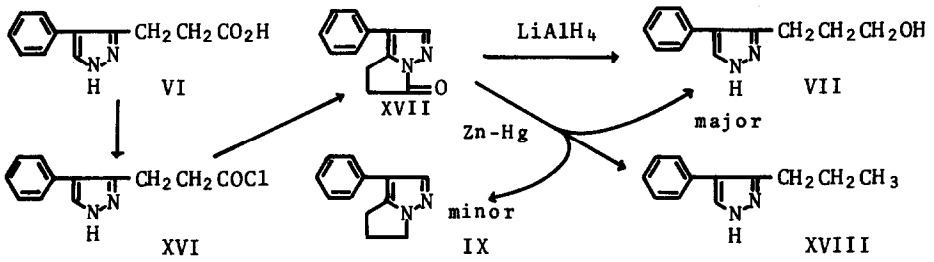
amino analogue of withasomnine, 4-(2'-aminophenyl)-1,5-trimethylenepyrazole(XV), m.p.109-110.5°, was obtained.

The compound XV was submitted to diazotization and to subsequent de-amination to yield the ultimate product, 4-phenyl-1,5-trimethylenepyrazole(IX).

Thus we were able to synthesize withasomnine(IX) by Method B, too.

Besides those practical synthetic methods A and B, we have also established the following method (Scheme 3).

Scheme 3



4-Phenyl-3-pyrazolepropionic acid(VI) prepared by Method A was converted to the acid-chloride(XVI) with thionyl chloride and then to the lactam (XVII), m.p.181-183° with triethylamine. When the lactam XVII was submitted to $LiAlH_4$ reduction, we didn't obtain IX but the ring-opening reduced product(VII). While, submitting the lactam XVII to Clemmensen reduction the required product IX was afforded as a minor product and simultaneously, the ring-opening products VII and XVIII as major products.

References and Notes

[1] H.-B. Schröter, D. Neumann, A. R. Katritzky and F. J. Swinbourne: Tetrahedron, 22, 2895 (1966).

[2] W. C. Anthony: J. Org. Chem., 25, 2049 (1960).

[3] C. Alberti: Gazz. chim. ital., 87, 720 (1957).

* Method A and Method B : Patent pending (1967, Japan).

After this communication had been contributed, Mr. T. Onaka (ITZUU Laboratory, Tokyo) kindly informed us that he had also completed a synthesis of withasomnine by his own method. Further, our identification was confirmed by mixed m.p. and IR spectral comparison with natural withasomnine, through the kindness of T.Onaka ,to whom the authors' thanks are due.