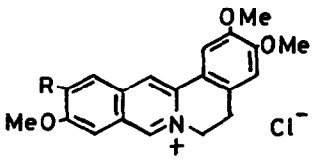
Tetrahedron Letters No. 19, pp 1597 - 1600, 1976. Pergamon Press. Printed in Great Britain.

# A NOVEL AMINATION OF ISOQUINOLINIUM SALTS VIA NUCLEOPHILIC SUBSTITUTION REACTION

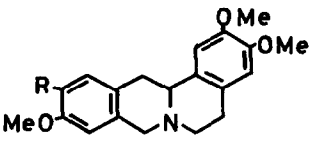
Shunsuke Naruto*, Hiroyuki Mizuta and Haruki Nishimura
Research Laboratories, Dainippon Pharmaceutical Co., Ltd.
Enoki-cho, Suita, Osaka 564, Japan

(Received in Japan 10 March 1976; received in UK for publication 22 March 1976)

The Smiles rearrangement at the $C_9$-position of protoberberinium salt[1] prompted us to examine a substitution reaction at that position. We now wish to report a new and unusual amination of 6- or 8-alkoxyisoquinolinium salts. Treatment of such salts with primary amines produces 6- or 8-aminoisoquinolinium derivatives. The reaction proceeded in refluxing ethanol or in refluxing methanol for 2 to 72 hours using 4 to 40 folds moles of amine, e.g., a mixture of dehydrocorydaline chloride(1a)(0.2 g), ethanolamine(2 ml) and ethanol(6 ml) was refluxed for 2 hr to give 9-(2-hydroxyethyl)amino derivative(2a)[2], mp 242-245°(dec), in 90% yield, whose bromide(2b), mp 233-236°(dec), was identified with the Smiles rearrangement product(2b)[1]. Other examples of this reaction are shown in TABLE. Using benzylamine, 2,3,10,11-tetramethoxy-5,6-dihydrodibenzo[a,g]quinolizinium chroride(3), mp 220-222°(dec), obtained from dl-xylopinine(5a)[3] gave 11-benzylamino derivative(4), mp 245-250°(dec). Reduction of 4 with sodium borohydride in methanol followed by catalytic debenzylation led to the known 11-amino-tetrahydroprotoberberine derivative(5b)[4], mp 225-228°.

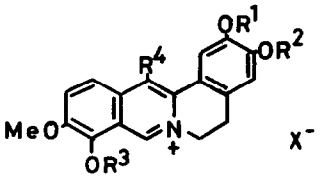



3 R=OMe
4 R=NHCH$_2$C$_6$H$_5$




5a R=OMe
5b R=NH$_2$

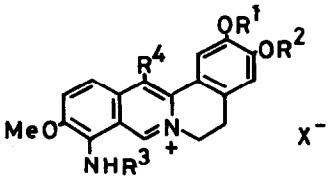
The $C_9$- and $C_{11}$-positions of protoberberinium salts are respectively corresponding to the $C_8$- and $C_6$-positions of isoquinolinium salts(6) being as an essential partial structure for this amination. These positions are activated by the presence of $C=\overset{+}{N}=$ group and the $C_6$-position of 6 is considered to be in less steric hindrance than the $C_8$-position of 6.



1

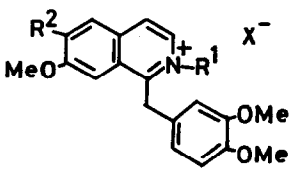
| | $R^1$ | $R^2$ | $R^3$ | $R^4$ | X |
|---|---|---|---|---|---|
| 1a | Me | Me | Me | Me | Cl |
| 1b | Me | Me | Me | H | $CH_3SO_4$ |
| 1c | $-CH_2-$ | | Me | Me | Cl |
| 1d | $-CH_2-$ | | Me | H | Cl |
| 1e | Me | Me | Pr | Me | Cl |
| 1f | Me | Me | By | Me | Br |
| 1g | Me | Me | H | Me | Cl |

Me: $CH_3$
Pr: $CH_2CH_2CH_3$
By: $CH_2C_6H_5$



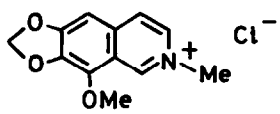
2

| | $R^1$ | $R^2$ | $R^3$ | $R^4$ | X |
|---|---|---|---|---|---|
| 2a | Me | Me | $CH_2CH_2OH$ | Me | Cl |
| 2b | Me | Me | $CH_2CH_2OH$ | Me | Br |
| 2c | Me | Me | $CH(CH_3)CH_2CH_3$ | Me | Cl |
| 2d | Me | Me | $CH_2CH_2NH_2 \cdot HCl$ | Me | Cl |
| 2e | Me | Me | Pr | Me | Cl |
| 2f | Me | Me | By | Me | Cl |
| 2g | Me | Me | $CH_2By$ | Me | Cl |
| 2h | Me | Me | By | H | $CH_3SO_4$ |
| 2i | $-CH_2-$ | | $CH_2CH_2OH$ | Me | Cl |
| 2j | $-CH_2-$ | | By | H | Cl |

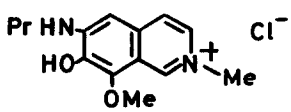


7

| | $R^1$ | $R^2$ | X |
|---|---|---|---|
| 7a | Me | OMe | I |
| 7b | By | OMe | Br |
| 7c | Me | NHPr | I |
| 7d | Me | $NHCH_2CH_2OH$ | I |
| 7e | Me | NHBy | Br |
| 7f | By | NHBy | I |
| 7g | Me |  | I |

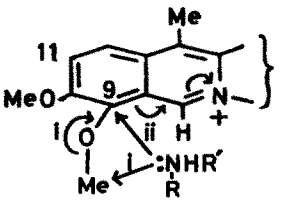


8



9

6



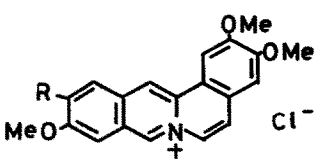
1a-A i: demethylation
ii: amination

To test the generality of this amination, N-methylpapaverinium iodide(7a) was treated with propylamine. 6-Propylamino derivative(7c), mp 210-215°(dec), was obtained in 90% yield. Other amino-papaverine derivatives obtained by this route are indicated in TABLE. Amination of O-methyltarconine chloride(8)[5] with propylamine afforded predominantly one product(9), characterized as picrate, mp 166-168°, $\nu_{NH}^{CHCl_3}$ 3320 $cm^{-1}$, $\nu_{OH}^{CHCl_3}$ 3400 $cm^{-1}$, in 85% yield, in which the methylenedioxy group of 8 was cleavaged to form an ortho-hydroxypropylamino group.

On the other hand, an attempted amination of 1a with pyrrolidine gave 9-desmethyldehydrocorydaline(1g)[1] in 90% yield besides N-methyl-pyrrolidine whose picrate was identified with an authentic sample. Other secondary amines and tert.-butylamine reacted with 1a as well as pyrrolidine. Using sec.-butylamine, 1a afforded two products, 9-sec.-butylamino derivative(2c), mp 238-240°(dec)(yield, 20%) and 1g(64%). From these results, it depends on the steric factor of the using amine whether the nucleophiles attack the $C_9$-position or the $CH_3$(Me)-group of $C_9$-OMe group of 1a as shown in 1a-A. Amination of 7a with pyrrolidine gave 6-pyrrolidino derivative(7g), mp 235-238°(dec), in 45% yield because of the less steric hindrance at that position as described above.

In a related experiment, norcoralyne chloride(10)[3] was refluxed in methanol with benzylamine for 72 hours to generate predominantly one product(11), mp 245-247°(dec), in 85% yield. Reduction of 11 as in the case of 4 afforded 5b confirming the aminated position.

Further investigation on this amination is in progress.



10 R=OMe

11 R=$NHCH_2C_6H_5$

TABLE [2]

| Starting Salt | Amine | Solvent/ Reaction Time | Product | Yield | mp °C(dec) |
|---|---|---|---|---|---|
| 1a | $H_2NCH_2CH_2NH_2$ | EtOH/ 2 hr | 2d | 90% | 187-190 |
| 1a | $PrNH_2$ | MeOH/ 3 hr | 2e | 90% | 214-215 |
| 1a | $ByNH_2$ | EtOH/ 5 hr | 2f | 86% | 227-228 |
| 1a | $ByCH_2NH_2$ | EtOH/ 4 hr | 2g | 87% | 205-206 |
| 1b | $ByNH_2$ | EtOH/ 2 hr | 2h | 85% | 186-187 |
| 1c | $H_2NCH_2CH_2OH$ | EtOH/50 hr | 2i | 60% | 250-255 |
| 1d | $ByNH_2$ | MeOH/72 hr | 2j | 60% | 269-271 |
| 1e | $H_2NCH_2CH_2OH$ | EtOH/ 3 hr | 2b | 67% | 233-236 |
| 1f | $H_2NCH_2CH_2OH$ | EtOH/ 4 hr | 2b | 67% | 233-236 |
| 7a | $H_2NCH_2CH_2OH$ | EtOH/ 7 hr | 7d | 90% | 215-217 |
| 7a | $ByNH_2$ | EtOH/ 6 hr | 7e | 90% | 225-230 |
| 7b | $ByNH_2$ | EtOH/ 8 hr | 7f | 70% | 140-145 |

## References


1) S. Naruto, H. Mizuta, J. Nakano and H. Nishimura, Tetrahedron Letters, preceding paper in this issue.

2) All new compounds had analytical data consistent with the assigned structures and have been additionally characterised as tetrahydro-derivatives after reduction with sodium borohydride. The yields quoted are for pure products.

3) T. Kametani, M. Takeshita, F. Satoh and K. Nyu, Yakugaku Zasshi, 84, 478(1974).

4) S. Ishiwata and K. Itakura, Chem. Pharm. Bull.(Tokyo), 18, 763(1970). Lit. mp 225-228°. The spectral data of 5b were identical with those of the reported data.

5) J. Knabe, Arch. Pharm., 293, 121(1960).