

ELECTROREDUCTIVE SYNTHESIS OF 1-(BROMOBENZYL)-ISOQUINOLINE DERIVATIVES
AND ITS APPLICATION TO CULARINE SYNTHESIS¹

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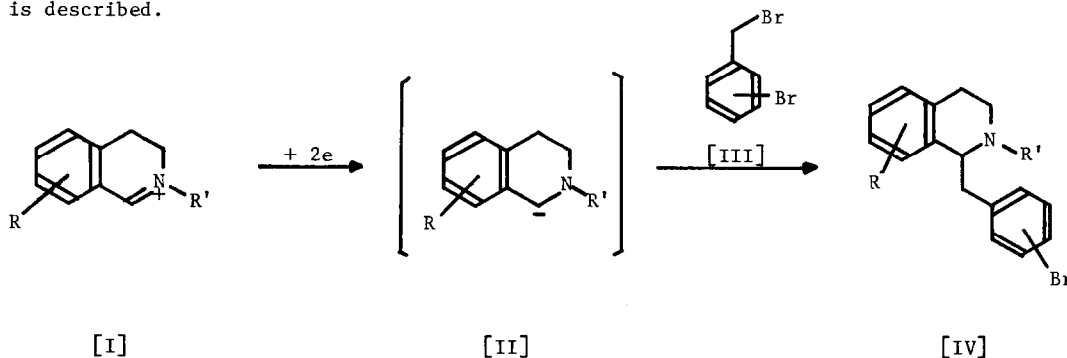
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Electrochemical reduction of immonium salts in the presence of bromobenzylbromide derivatives gave 1-(bromobenzyl)-isoquinoline derivatives in moderate yields. This reaction is useful in the synthesis of several natural alkaloids as exemplified in the synthesis of Cularine.

Although 1-(bromobenzyl)-isoquinoline derivatives are useful intermediates in the synthesis of Cularine,² Aporphine,³ Dibenzopyrrocoline,⁴ Berbine,⁵ and Bisbenzylisoquinoline,⁶ their synthesis has not necessarily been established. The synthetic methods hitherto known are mainly the bromination of the benzyl moiety of 1-benzyl-isoquinoline derivatives, and hence the reaction is rather lack of selectivity and generality.

In the present study, a new and simple method of 1-(bromobenzyl)-isoquinoline synthesis through electroreduction⁷ of immonium salts [I]⁸ and bromobenzylbromides [III]⁹ at -1.8 V vs. SCE is described.



Our new method is highly versatile as summarized in Table I.

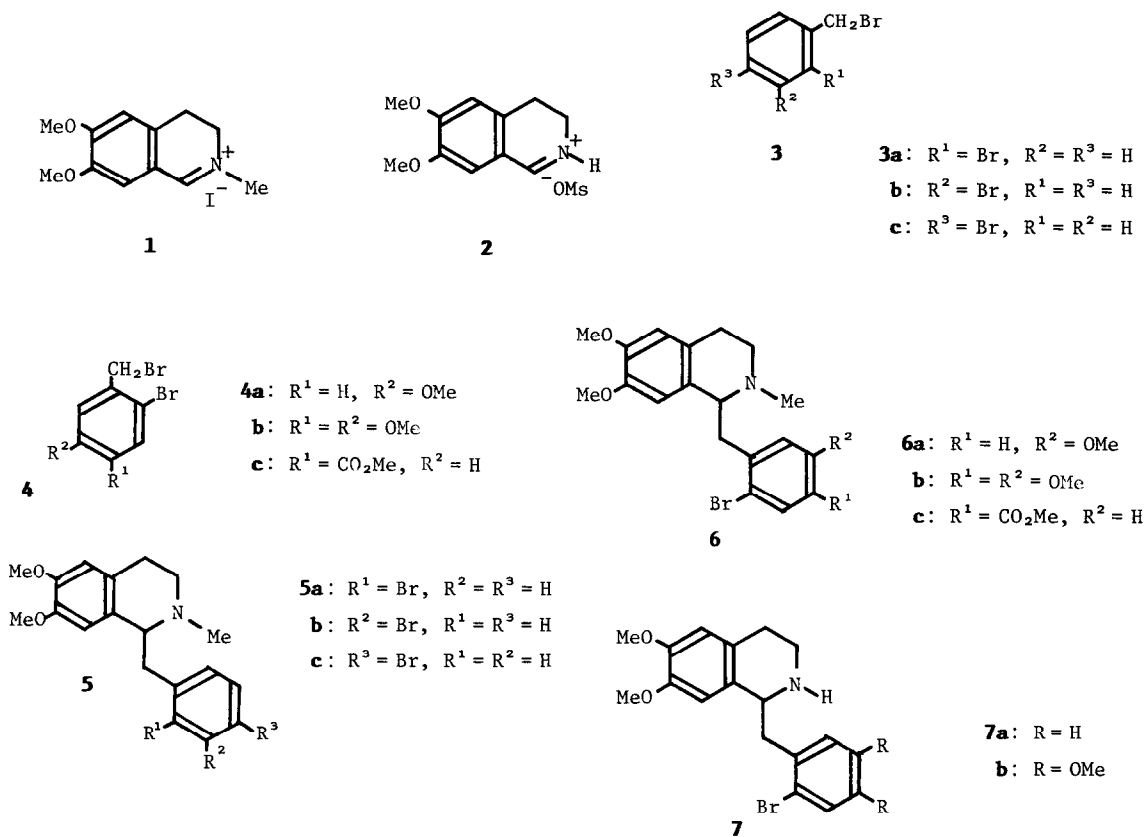
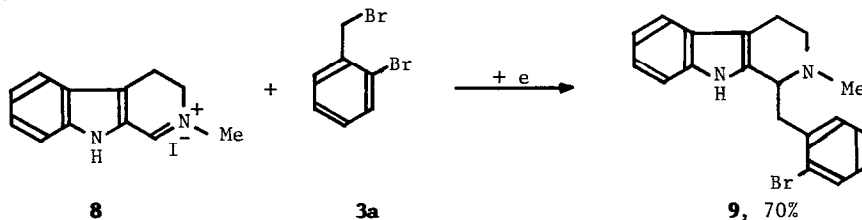


Table I. Reaction of Immonium Salts with Bromobenzylbromides.

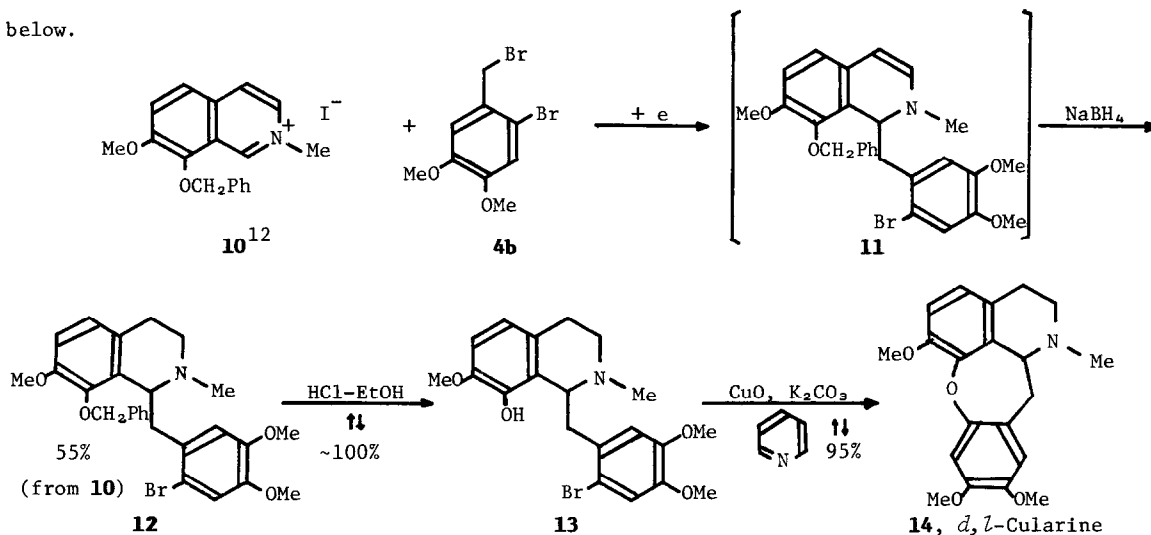
Immonium Salts	Bromobenzylbromides	Products	Yields (%)
1	3a	5a	65
1	3b	5b	47
1	3c	5c	48
1	4a	6a	61
1	4b	6b	51
1	4c	6c	60
2	3a	7a	50
2	4b	7b	53

It is noteworthy that the anions [II] generated from immonium salts [I] react selectively with the bromomethyl moiety of the bromobenzylbromide [III].

Furthermore, our method is applicable to indole derivatives as well as isoquinoline derivatives.



A new synthesis of Cularine could be performed by using this simple method as depicted below.



The electroreduction of an immonium salt (**10**)^{7a} at -2.0 V *vs.* SCE in the presence of a bromobenzylbromide (**4b**) followed by NaBH₄ reduction of the resulting enamine (**11**) afforded a product **12**. Debenzylation of **12** to a phenolic compound **13** in ethanolic hydrochloric acid solution¹³ and subsequent Ullmann reaction¹⁴ by CuO in pyridine gave *d,l*-Cularine (**14**),¹⁴ the total yield from **10** being 52%.

Although yields of our new benzylation reaction are not always satisfactory, the simplicity and versatility of the electrochemical reaction make this new synthesis promising.

Acknowledgement

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References and Notes

- 1) *Electroorganic Chemistry*. 51.
- 2) a) T. Kametani, K. Fukumoto, and M. Fujihara, *Chem. Pharm. Bull.*, **20**, 1800 (1972).
b) H. Iida, H. C. Hsu, and T. Kikuchi, *ibid.*, **21**, 1001 (1973).
- 3) a) A. H. Jackson and J. A. Martin, *J. Chem. Soc. (C)*, **1966**, 2061.
b) T. Kametani, S. Shibuya, K. Kigasawa, M. Hiragi, and O. Kusama, *ibid.*, **1971**, 2712.
- 4) a) T. Kametani and K. Ogasawara, *J. Chem. Soc. (C)*, **1967**, 2208.
b) F. Benington and R. D. Morin, *J. Org. Chem.*, **32**, 1050 (1967).
- 5) a) T. Kametani and M. Ihara, *J. Chem. Soc. (C)*, **1967**, 530.
b) C. Tani, S. Takao, H. Endo, and E. Oda, *J. Pharm. Soc. Jpn.*, **93**, 268 (1973).
- 6) a) T. Kametani, H. Iida, and K. Sakurai, *J. Chem. Soc. (C)*, **1971**, 1024.
b) R. W. Doskotch, J. D. Phillipson, A. B. Ray, and J. L. Beal, *J. Org. Chem.*, **36**, 2409 (1971).
- 7) a) T. Shono, K. Yoshida, K. Ando, Y. Usui, and H. Hamaguchi, *Tetrahedron Lett.*, **1978**, 4819.
b) T. Shono, Y. Usui, T. Mizutani, and H. Hamaguchi, *ibid.*, **21**, 3073 (1980).
- 8) Immonium salts were prepared according to the established method.⁷
- 9) 2-Bromo-5-methoxybenzylbromide (**4a**) was prepared according to the reported method.¹⁰
Other derivatives of bromobenzylbromides (**3a-c**, **4b,c**) were synthesized by bromination of their bromotoluene derivatives¹¹ by NBS.
- 10) R. Breslow, S. Garratt, L. Kaplan, and D. LaFollette, *J. Am. Chem. Soc.*, **90**, 4051 (1968)
- 11) The starting bromotoluene derivatives were prepared according to the reported method.
4b. T. Heap, T. G. H. Jones, and R. Robinson, *J. Chem. Soc.*, **1927**, 2021.
4c. A. M. Fleifel, *J. Org. Chem.*, **25**, 1024 (1960).
- 12) A. H. Jackson, G. W. Stewart, G. A. Charnock, and J. A. Martin, *J. Chem. Soc., Perkin Trans 1*, **1974**, 1911.
- 13) H. Iida, T. Kikuchi, K. Sakurai, and T. Watanabe, *J. Pharm. Soc. Jpn.*, **89**, 645 (1969).
- 14) S. Ishiwata, T. Fujii, N. Miyaji, Y. Satoh, and K. Itakura, *Chem. Pharm. Bull.*, **18**, 1850 (1970).

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