APPLICATION OF REISSERT COMPOUNDS TO THE TOTAL SYNTHESIS OF ISOQUINOLINE ALKALOIDS AND RELATED COMPOUNDS

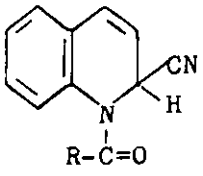
Frank D. Popp

Department of Chemistry, Clarkson College of Technology

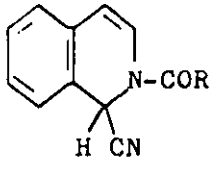
Potsdam, New York 13676, U.S.A.

N-Acyldihydroisoquinaldonitriles (isoquinoline Reissert compounds) have been used as the key intermediates in the synthesis of a wide variety of isoquinoline alkaloids.

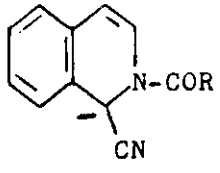
The chemistry of N-acyldihydroquinaldonitriles (1) and N-acyldihydroisoquinaldonitriles (2) (Reissert compounds) has been the subject of two comprehensive reviews.[1-2] An important application of the chemistry of isoquinoline Reissert compounds (2) is in the field of isoquinoline alkaloid syntheses and this review gives a survey of the work carried out in that area.



(1)



(2)

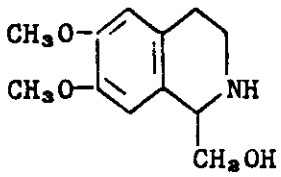


(3)

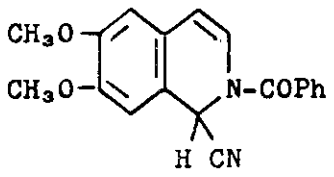
While a number of methods exist for the formation of isoquinoline Reissert compounds[1-2] the most general method involves

reaction of an isoquinoline, an acyl chloride, and potassium cyanide in a methylene chloride-water solvent system.[3] The reactions of isoquinoline Reissert compounds that have been applied to isoquinoline alkaloids syntheses all involve generation of the conjugate base 3 from the Reissert compound. The most convenient and general method of formation of this anion involves the use of sodium hydride in dimethylformamide[4-5] although other reagents such as, for example, phenyllithium in ether-dioxane[1-2] have been used.

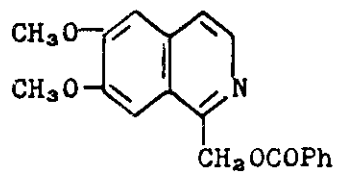
The alkaloid calycotomine (4) has been prepared from 2-benzoyl-6,7-dimethoxy-1,2-dihydroisoquinaldonitrile (5).[6] As will be noted throughout the review this Reissert compound has proven to be a valuable starting point for the synthesis of a number of alkaloids. Reaction of the anion of 5 with formaldehyde gave the



(4)



(5)

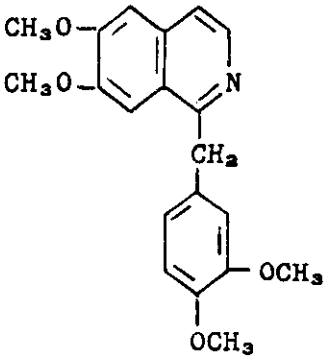


(6)

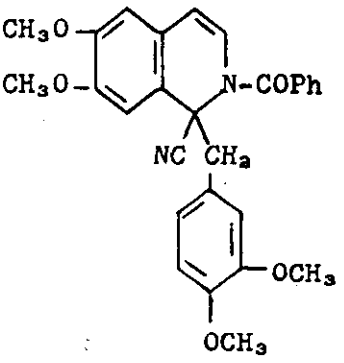
ester 6. Hydrolysis of 6 followed by catalytic hydrogenation gave calycotomine (4). The overall yield of calycotomine from beta-(3,4-dimethoxyphenyl)ethylamine (the precursor of the 6,7-dimethoxyisoquinoline used to form 5) was 44%[6] which was a great improvement over the yield obtained in other synthetic routes to this alkaloid.

A wide variety of benzylisoquinoline alkaloids and related compounds have been prepared from Reissert compounds. The first

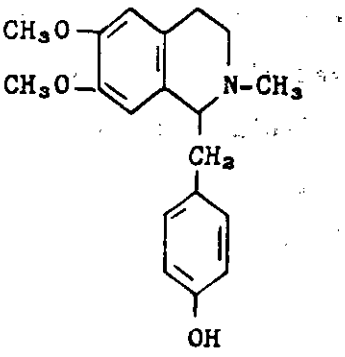
alkaloid synthesized using a Reissert compound as an intermediate was papaverine (7).[7] Reaction of the anion of 5 with 3,4-dimethoxybenzyl chloride gave the condensation product 8 which was cleaved with alkali to give papaverine (7). Use of 3,4-dimethoxybenzaldehyde with the anion of 5 followed by hydrolysis gave rise to papaverinol.[7] Also prepared from 5 was armepavine (9), in 44%



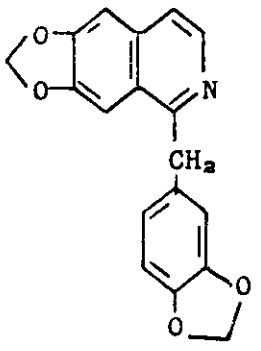
(7)



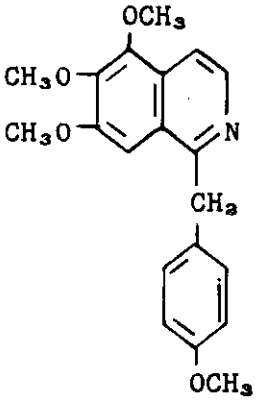
(8)



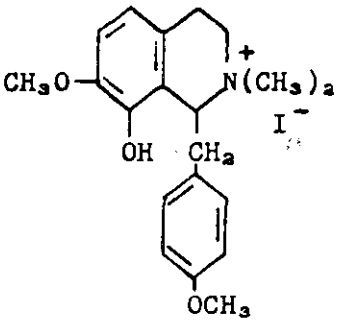
(9)



(10)



(11)



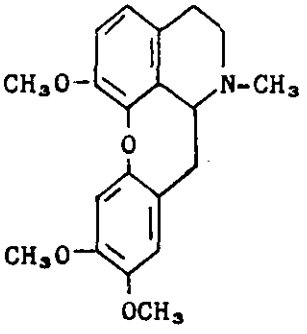
(12)

overall yield from beta-(3,4-dimethoxyphenyl)ethyl amine, using p-benzyloxybenzaldehyde in the condensation with the anion of 5.[8] Alkylation of the anion of 2-benzoyl-6,7-methylenedioxy-1,2-dihydroisoquinaldonitrile with 3,4-methylenedioxybenzyl chloride

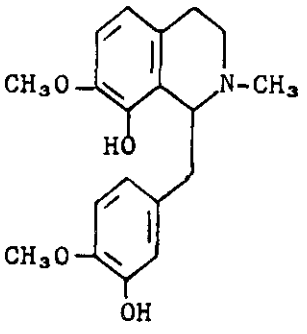
followed by hydrolysis gave escholamine (10) in a 60% yield from 6,7-methylenedioxyisoquinoline.[9] In a similar manner takatonine (11) has been obtained in a 75% yield from p-methoxybenzyl chloride and 5,6,7-trimethoxyisoquinoline.[9]

Petaline iodide (12) has been prepared from 7-methoxy-8-hydroxyisoquinoline by condensation of p-methoxybenzyl chloride with the isoquinoline Reissert compound followed by hydrolysis, methylation, reduction, and methylation.[10] In a similar sequence 7,8-dimethoxyisoquinoline Reissert compound was used to prepare O-methylpetaline iodide.[10] A variety of other substituted 1-benzylisoquinolines have also been prepared through the use of Reissert compounds.[11-17] The formation of a Reissert compound from phthalazine[18] has opened the way to prepare 1-benzyl-phthalazines[19] as phthalazine analogues of benzylisoquinoline alkaloids.

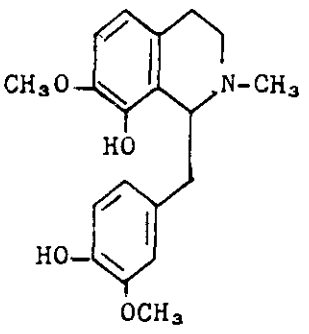
The alkaloid cularine (13) has been prepared by potassium ferricyanide oxidation of 14 followed by methylation.[20] The



(13)



(14)

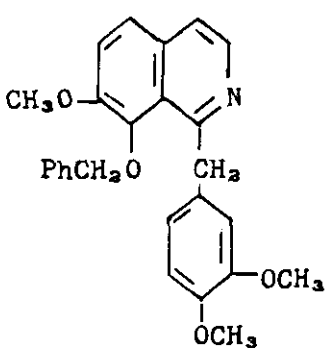


(15)

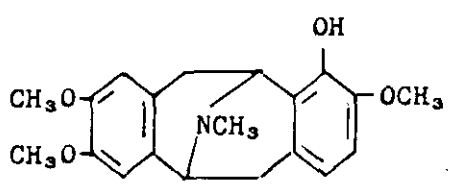
intermediate 14 was obtained by alkylation of the anion of the Reissert compound of 7-methoxy-8-benzyloxyisoquinoline with 4-

methoxy-3-benzyloxybenzyl chloride, followed by alkaline hydrolysis, methylation, reduction, and acid hydrolysis.[20] An unsuccessful attempt to obtain cularine (13) involved potassium ferricyanide oxidation of 15 prepared through a similar route from the same Reissert compound.[17] This oxidation led to a spirocyclic dienone which could not be rearranged to cularine.

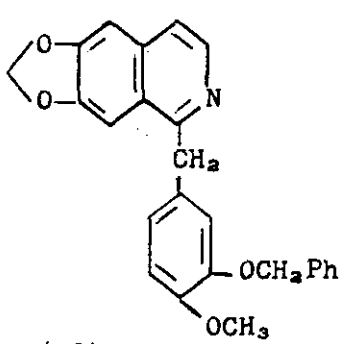
Benzylisoquinolines synthesized from Reissert compounds have been used in the pavine and isopavine alkaloid area. The isoquinoline 16 was prepared by alkylation of the Reissert compound derived from 7-methoxy-8-benzyloxyisoquinoline.[21] Methylation and reduction of 16 followed by treatment with formic acid-phosphoric acid led to the alkaloid platycerine (17).[21] The



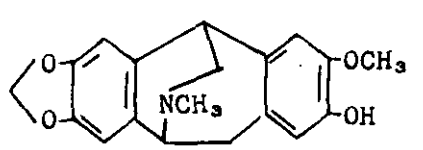
(16)



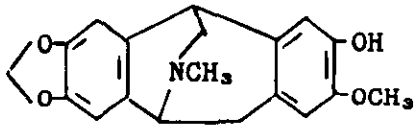
(17)



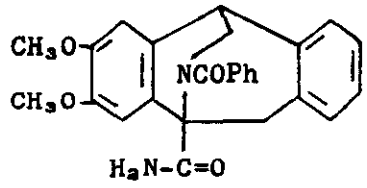
(18)



(19)

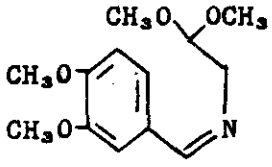


(20)

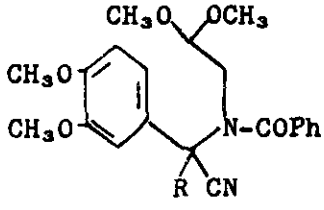


(21)

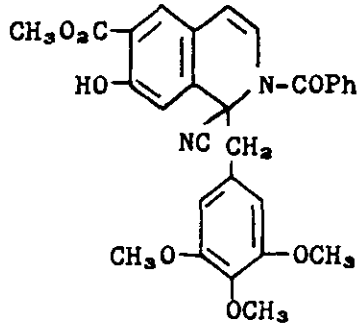
isoquinoline 18 which was obtained from 2-benzoyl-6,7-methylene-dioxy-1,2-dihydroisoquinaldonitrile in two steps was converted to the isopavine alkaloid amurensine (19) in four steps.[22] Use of 4-benzyloxy-3-methoxybenzyl bromide in place of 3-benzyloxy-4-methoxybenzyl bromide in the alkylation of the Reissert compound led eventually to the isomer 20.[22] The isopavine structure 21 was prepared in a novel sequence.[23] Treatment of the aminoacetal derivative 22 with benzoyl chloride and potassium cyanide gave



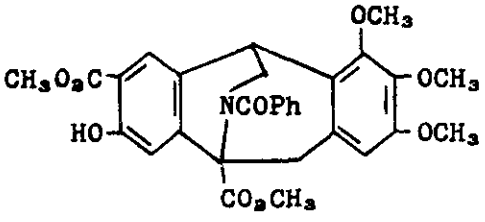
(22)



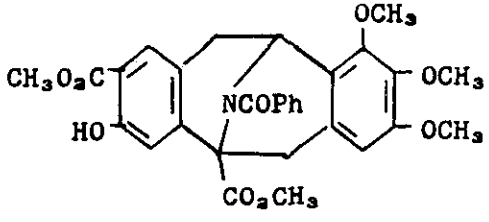
(23)



(26)



(24)

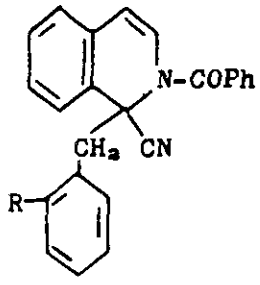


(25)

the Reissert compound analogue 23 (R = H) in 70% yield. Alkylation of 23 (R = H) with benzyl chloride and sodium hydride in

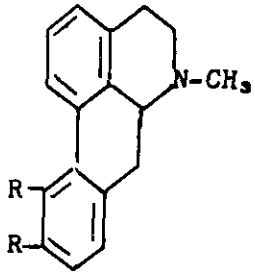
dimethylformamide gave 23 (R = CH_2Ph). Treatment of this alkylation product with alcoholic hydrochloric acid gave 21 rather than the expected isoquinoline derivative.[23] In another unexpected entry into this type of ring system, 24 or 25 was obtained as a side product during the treatment of alkylated Reissert compound 26 with sodium methoxide in methanol followed by methanolic hydrochloric acid.[13] The expected benzylisoquinoline was the major product.

The Reissert compound method has been used to synthesize a number of different types of aporphine alkaloids. In the first and simplest examples[24-25] isoquinoline Reissert compound (2, R = Ph) was treated with o-nitrobenzyl chloride and sodium hydride in dimethylformamide to give 27. Hydrolysis, methylation, reduction and the Pschorr reaction converted 27 to aporphine (28). Reaction of the Reissert anion with 3,4-dimethoxy-2-nitrobenzyl chloride and using an ether cleavage as the final step in the sequence led to apomorphine (29).[26] Alkylation of the isoquinoline



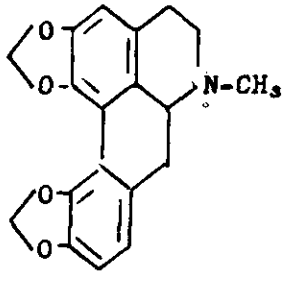
(27) R = NO_2

(30) R = I



(28) R = H

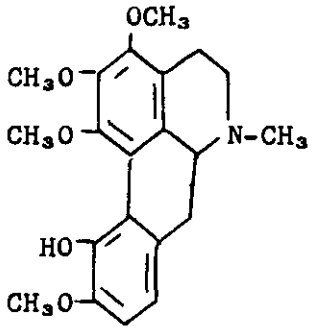
(29) R = OH



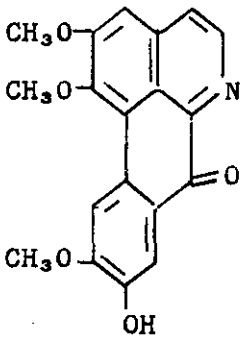
(31)

Reissert compound with o-iodobenzyl chloride gave 30 which could also be converted to aporphine[25] through a final step involving

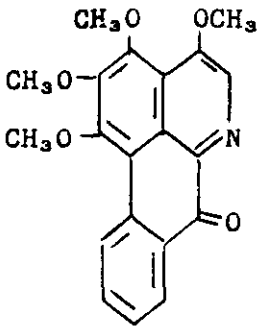
photochemical cyclization. The aporphine alkaloids: N-methylovigerine (31),[27] oconovine (32),[28] atheroline (33),[29] and imenine (34)[30] have all been synthesized with alkylation of a Reissert compound anion by an o-nitrobenzyl halide as the key step in the sequence. Care must be taken during the hydrolysis of the alkylated Reissert compound and Triton B is preferred to potassium hydroxide. Thus, for example, hydrolysis of 35 with Triton B leads to the desired 36 in the oconovine synthesis while hydrolysis of 35 with potassium hydroxide leads to 37.[28]



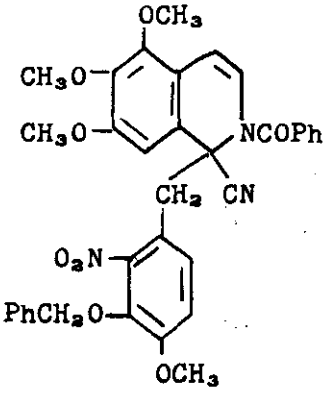
(32)



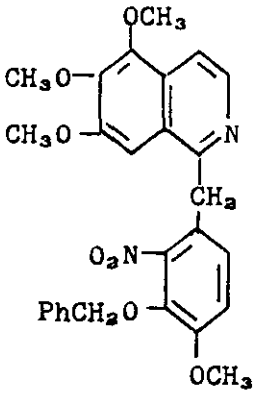
(33)



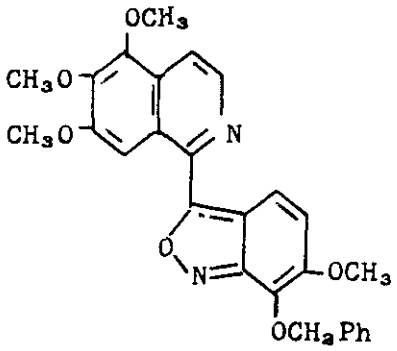
(34)



(35)



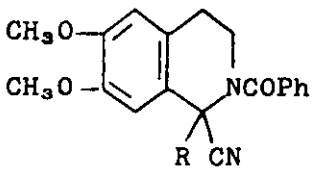
(36)



(37)

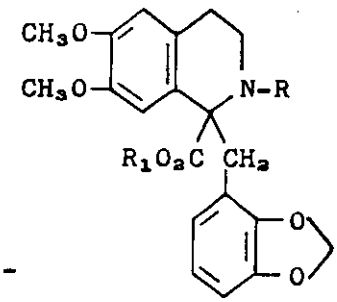
Reaction of 6,7-dimethoxy-3,4-dihydroisoquinoline with benzoyl

chloride and potassium cyanide gave the dihydro Reissert compound 38.[31] This dihydro Reissert compound underwent alkylation in the usual manner. Thus, for example, 2,3-methylenedioxybenzyl chloride and the anion of 38 gave 39.[31] A variety of compounds of the type 40 (R = H, CH_3, or PhCO; R_1 = H or CH_3) were prepared from 39 but all attempts at internal Friedel-Crafts acylation failed to yield 41 which was desired as an intermediate for the attempted synthesis of the alkaloid ochotensimine (42).[31]

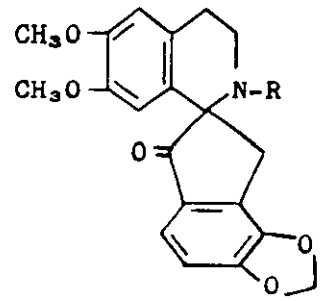


(38) R = H

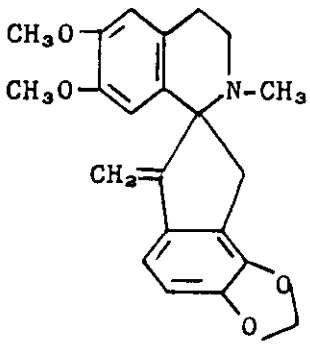
(39) R = 2,3-methylene-dioxybenzyl



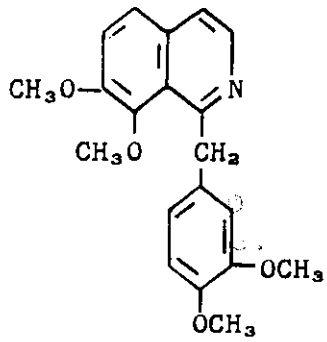
(40)



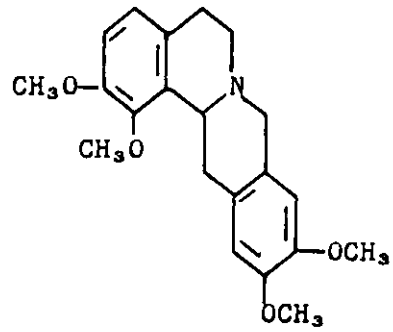
(41)



(42)



(43)

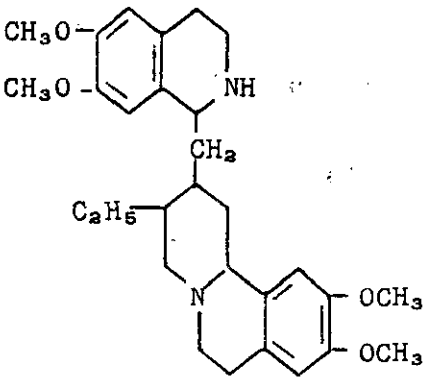


(44)

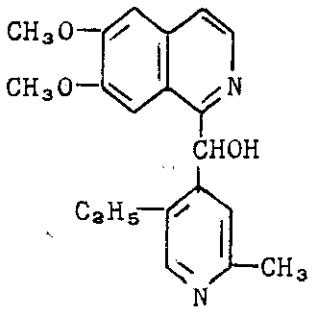
Alkylation of the anion of the 7,8-dimethoxyisoquinoline Reissert compound with 3,4-dimethoxybenzyl chloride gave, after hydrolysis, the benzylisoquinoline 43 which was converted to

casedine methyl ether (44) by hydrogenation and reaction with formaldehyde.[32]

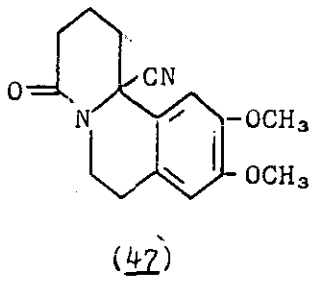
Although the alkaloid emetine (45) has not been synthesized by means of Reissert compounds, sveral approaches have been studied. Thus, compounds of the type 46[33] 47,[34] and 48[35-36] have been prepared by use of Reissert compounds.



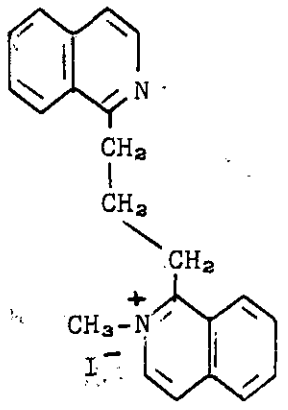
(45)



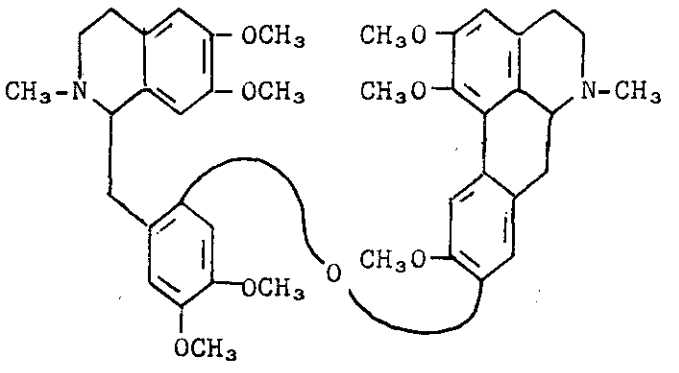
(46)



(47)



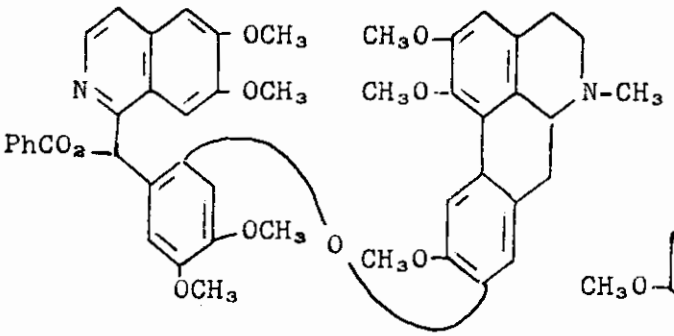
(48)



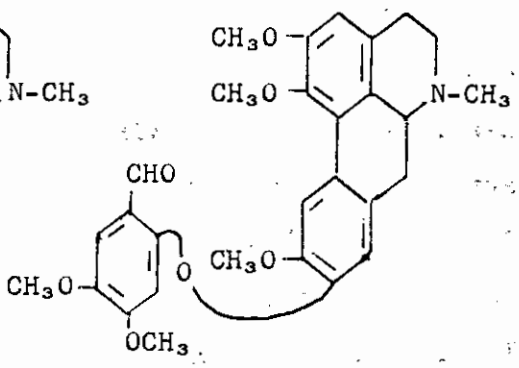
(49)

The antitumor alkaloid thalicarpine (49) has been synthesized through a route involving a Reissert compound.[37] The anion of 5

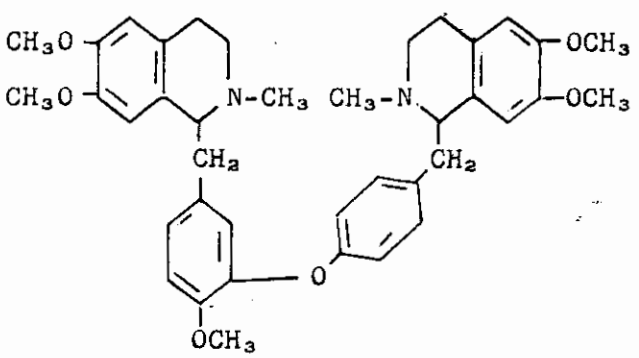
was reacted with 50 to give 51 which was then converted to thalicarpine (49) in two steps.[37]



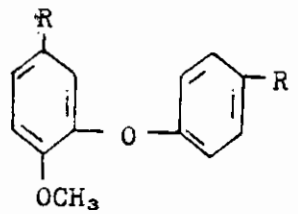
(51)



(50)

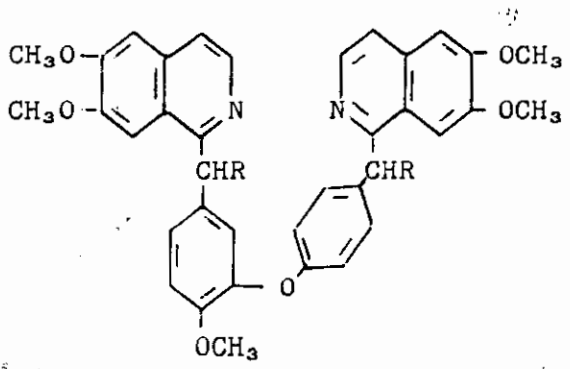


(52)



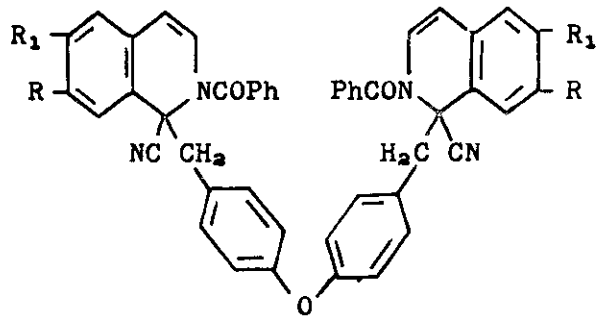
(53) R = CH_2Br

(54) R = CHO

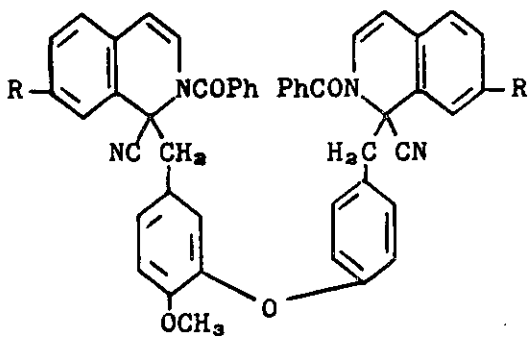


(55) R = H (56) R = OH

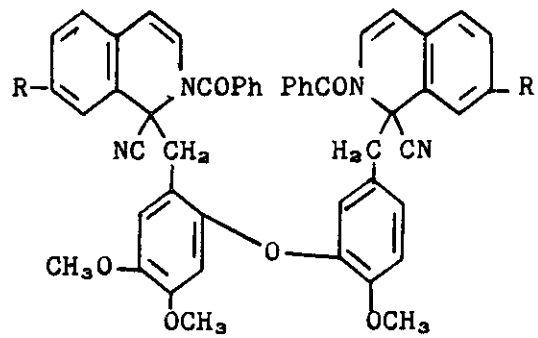
The bisbenzylisoquinoline O-methyldauricine (52) has been synthesized through the condensation of the anion of 5 with either 53 or 54 to give after hydrolysis 55 and 56 respectively.[38] Both 55 and 56 can be converted to O-methyldauricine (52). In the case of the path involving 54 and passing through 56, O-methyldauricine (52) was obtained in a 41% overall yield from beta-(3,4-dimethoxy)phenylethyl amine.[38] In a program directed towatds the synthesis of analogues of bisbenzylisoquinoline alkaloids the compounds 57, 58, and 59 have been prepared by alkylation of the appropriate Reissert compounds.[39] The base-



(57) (R_1 = R = H; R_1 = R = OCH_3; R_1 = H, R = OCH_3)



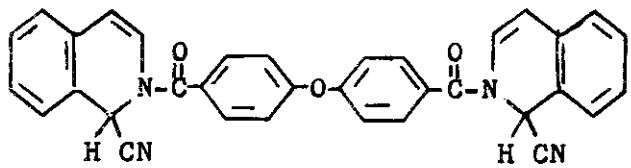
(58) (R = H; R = OCH_3)



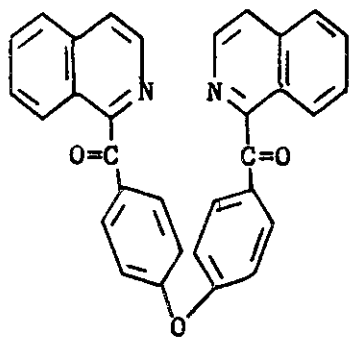
(59) (R = H; R = OCH_3)

catalyzed rearrangement of the acyl group of a Reissert compound from the 2-position to the 1-position of the isoquinoline[1-2] has

not met with much use in alkaloid syntheses. It should be noted, however, that in model studies[40] 60 appears to undergo rearrangement to 61 suggesting that further study of this route is in order.



(60)



(61)

It can be seen from the above survey that a wide variety of isoquinoline alkaloids have been prepared making use of a route involving Reissert compounds. Where yield data is available the route through Reissert compounds has generally been shown to give the alkaloids in good yield. In fact the overall yield through the Reissert compound route has in general been higher then the overall yield using the more classical methods of alkaloid synthesis. Another important use of the route through Reissert compounds is in the synthesis of analogues of a given alkaloid. Thus by using the Reissert compound from a single isoquinoline one can react its anion with a variety of substituted benzyl halides or benzaldehydes, or by using a single benzyl halide or benzaldehyde one can react it with the anions of a series of substituted isoquinoline Reissert compounds.

ACKNOWLEDGEMENT The unpublished results of F. D. Popp and co-workers were supported in part by a grant (CA-10965) from the National Cancer Institute.

REFERENCES

1 W. E. McEwen and R. L. Cobb, Chem. Revs., 1955, 55, 511.

2 F. D. Popp, Adv. Heterocycl. Chem., 1968, 9, 1.

3 F. D. Popp and W. Blount, J. Org. Chem., 1962, 27, 297.

4 F. D. Popp and J. M. Wefer, Chem. Commun., 1966, 207.

5 J. R. Kershaw and B. C. Uff, Chem. Commun., 1966, 331.

6 H. W. Gibson, F. D. Popp, and A. Catala, J. Heterocycl. Chem., 1964, 1, 251.

7 F. D. Popp and W. E. McEwen, J. Am. Chem. Soc., 1957, 79, 3773.

8 H. W. Gibson, F. D. Popp, and A. C. Noble, J. Heterocycl. Chem., 1966, 3, 99.

9 A. J. Birch, A. H. Jackson, and P. V. R. Shannon, Tetrahedron Letters, 1972, 4789.

10 B. C. Uff, J. R. Kershaw, and S. R. Chhabra, J. Chem. Soc., Perkin Trans. I, 1972, 479.

11 B. C. Uff and J. R. Kershaw, J. Chem. Soc. (C), 1969, 666.

12 J. Sam and A. J. Bej, J. Pharm. Sci., 1967, 56, 1441.

13 S. F. Dyke, A. W. C. White, and D. Hartley, Tetrahedorn, 1973, 29, 857.

14 H. W. Gibson and F. D. Popp, J. Chem. Soc. (C), 1966, 1860.

15 F. D. Popp and H. W. Gibson, J. Heterocycl. Chem., 1964, 1, 51.

16 F. D. Popp and J. M. Wefer, J. Heterocycl. Chem., 1967, 4, 183.

17 A. H. Jackson and G. W. Stewart, Tetrahedron Letters, 1971, 4941.

18 F. D. Popp, J. M. Wefer, and C. W. Klinowski, J. Heterocycl. Chem., 1968, 5, 879.

19 F. D. Popp and H. Heller, unpublished results.

20 A. H. Jackson and G. W. Stewart, Chem. Commun., 1971, 149.

21 F. R. Stermitz and D. K. Williams, J. Org. Chem., 1973, 38, 1761.

22 S. F. Dyke and A. C. Ellis, Tetrahedron, 1972, 28, 3999.

23 S. F. Dyke and A. C. Ellis, Tetrahedron, 1971, 27, 3803.

24 J. L. Neumeyer, B. R. Neustadt, and J. W. Weintraub, Tetrahedron Letters, 1967, 3107.

25 J. L. Neumeyer, K. H. Oh, K. K. Weinhardt, and B. R. Neustadt, J. Org. Chem., 1969, 34, 3786.

26 J. L. Neumeyer, B. R. Neustadt, and K. K. Weinhardt, J. Pharm. Sci., 1970, 59, 1850.

27 M. P. Cava and M. Srinivasan, Tetrahedron, 1970, 26, 4649.

28 M. P. Cava and M. V. Lakshmikantham, J. Org. Chem., 1970, 35, 1867.

29 M. P. Cava and I. Noguchi, J. Org. Chem., 1972, 37, 2936.

30 M. P. Cava and I. Noguchi, J. Org. Chem., 1973, 38, 60.

31 M. Shamma and C. D. Jones, J. Org. Chem., 1970, 35, 3119.

32 M. P. Cava, M. V. Lakshmikantham, and M. J. Mitchell, J. Org. Chem., 1969, 34, 2665.

33 F. D. Popp and W. E. McEwen, J. Am. Chem. Soc., 1958, 80,

1181.

34 H. W. Gibson, D. K. Chesney, and F. D. Popp, J. Heterocycl. Chem., 1972, 9, 541.

35 F. D. Popp, C. W. Klinowski, R. Piccirilli, D. H. Purcell, Jr., R. F. Watts, J. Heterocycl. Chem., 1971, 8, 313.

36 F. D. Popp and R. Piccirilli, unpublished results.

37 S. M. Kupchan and A. J. Liepa, Chem. Commun., 1971, 599.

38 F. D. Popp, H. W. Gibson, and A. C. Noble, J. Org. Chem., 1966, 31, 2296.

39 F. D. Popp and D. Smith, unpublished results.

40 F. D. Popp and R. Buhts, unpublished results.

Received, 21st June, 1973