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SYNTHESES OF (-)-PHYSOSTIGMINE, WITH PARTICULAR EMPHASIS UPON THE CLARIFICATION OF TWO ENIGMATIC EARLY SYNTHETIC APPROACHES*

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Abstract - Following a synopsis of the studies whereby the structure, including absolute configuration, of (-)-physostigmine – a metabolite from diverse botanical and also microbial sources - was established, the pharmacology and clinical uses of the alkaloid, its enantiomer and its hydrolysis product, (-)-eseroline, are briefly but comprehensively discussed. Synthetic approaches to (-)-physostigmine and its 1,2,3,3a,8,8a-hexahydro-3a-methylpyrrolo[2,3-*b*]indole ring system are then considered, with particular emphasis upon the early endeavors in this area by three independent groups and the interpretation of the results obtained by one of them.

The ripe seeds of *Physostigma venenosum* (Calabar beans) were used - probably for centuries - as an ordeal poison in trials for witch-craft and to effect ritualistic killings in the cruel and superstitious society that once prevailed in southeastern Nigeria[1] (NOTE 1). Their major toxic component, (-)-physostigmine[1-4] (NOTE 2), was first isolated in a pure but only in an amorphous, varnish-like state in 1864,[5] obtained in a crystalline form the following year[6] and was subsequently found to be dimorphous.[7]

The elucidation of its structure attracted much attention until two groups, namely Edgar Stedman with George Barger[8] (based upon a suggestion by Robert Robinson) and, somewhat tentatively, the Polonovski brothers[9,10] independently and almost simultaneously hypothesized it as **1**. However, the establishment of its absolute configuration as **2** (R = MeNH-CO, X = NMe)[11-13] had to wait some further forty-five years, despite the alkaloid's emerging diverse clinical utility.

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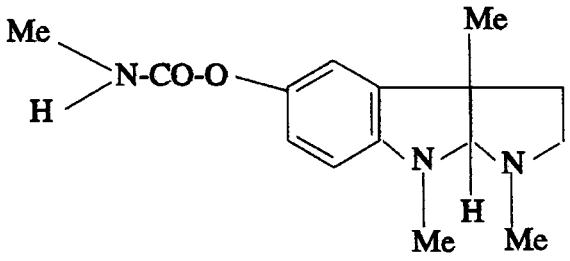
*Alkaloids of *Physostigma venenosum*, Part 12. For Part 11, see P. A. Crooks, B. Robinson, and O. Meth-Cohn, *Phytochem.*, 1976, **15**, 1092.



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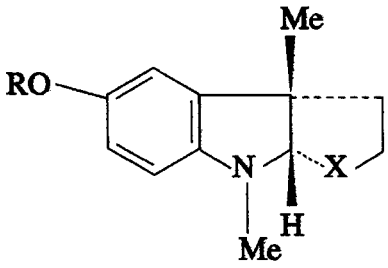

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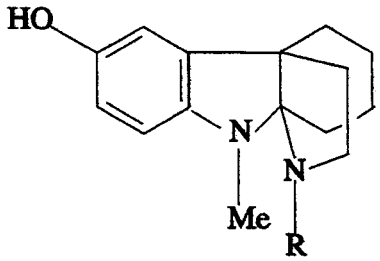
As well as playing roles in the cure and alleviation of disease, several alkaloidal drugs - such as atropine, curare, muscarine and nicotine - have also found use as tools in the elucidation of physiological and pharmacological mechanisms.[1] In accord with this, (-)-physostigmine played an important role in the discovery of the mechanism of neurohumoral transmission when it was recognized as a reversible inhibitor, *in vitro* and *in vivo*, of acetylcholinesterase.[1,3] This was one of the first examples whereby the mechanism of action of a drug could be defined at the molecular level relatively simply and (-)-physostigmine was the first alkaloid that was proven to exert its pharmacological activity through the inhibition of an enzyme.[1,3]

It is also the reason for its use in the treatment of a variety of neurological disorders associated with irregularities in cholinergic transmission, in which augmentation of cholinergic activity has proved to be of value. Thus it has found use as a miotic in the reduction of intraocular pressure in glaucoma[1,14-17] (and in alternation with a mydriatic such as atropine has also proved useful for the breaking of adhesions between the iris and the lens or cornea[17]) and offers a treatment for *myasthenia gravis*[1,14,17,18] (so-called[18] "The Miracle at St. Alfege's"), "intestinal atony"[19] and "urinary retention".[19] It is also established for the relief of central cholinergic intoxication from anticholinergic agents such as atropine (and related antimuscarinic drugs[14,15,17]) and curare (decurarization in anaesthesiology)[1] and from overdoses of tricyclic antidepressants,[14,15,17] phenothiazines,[14,17] antihistamines,[14,15,17] antipsychotics,[15] benzodiazepines,[15,17] and asthma powders (stramonium) and sleeping preparations[17] and as a prophylactic against the lethal effects of Soman, Sarin and Tabun (all three of which are extremely toxic "nerve gases" and are amongst the most potent of known synthetic poisons[14]) and other organophosphates.[14,15] Activity is also shown as an insecticide[20-22] - albeit a rather poor one[1] although (-)-physostigmine can be considered as the prototype of the insecticidal carbamates[1] - and a bactericide.[20] Furthermore, it has recently been employed in the treatment of paraplegic anejaculation[23-25] and has also generated considerable interest as a memory- and cognition-enhancing agent.[15,17,26] In particular its phenylcarbamate analogues such as

phenserine, tolserine and cymserine (**2**, R = Ph-NH-CO, 2-MeC_6H_4-NH-CO and 4-$Me_2CHC_6H_4$-NH-CO, respectively, X=NMe), which have increased lipophilicity and hence increased ability to cross the blood-brain barrier, have antiamnesic activity in dementia of the Alzheimer's type[27] (NOTE 3).

Notwithstanding all the above, its enantiomer, synthetic (+)-physostigmine, although possessing considerably lower antiacetylcholinesterase activity than the natural base,[15,28-31] still prevents organophosphate-induced damage at the neuromuscular synapse - by a mechanism unrelated to cholinesterase carbamoylation[30,31] - and offers prophylactic protection against otherwise lethal doses of Sarin.[30]

Additionally, its hydrolysis product, (-)-eseroline (**2**, R = H, X = NMe) - the synthesis of which can be greatly improved by alcoholysis of (-)-physostigmine in boiling butanol under reflux in the presence of sodium butoxide with subsequent product isolation as the fumarate salt,[31,32] exhibits antinociceptive activity,[31-34] as do synthetic analogues such as (-)-7-bromoeseroline ("a potent, centrally acting analgesic, with excellent oral activity and stability, and superior to morphine in its antinoceptive effects in rodents with significantly reduced side effects",[35] and a potent morphine-like analgesic, the agonist actions of which are μ-receptor mediated but which may have antagonist actions at the X- and δ-receptors as well,[37]) and a series of echibolines (**3**) (R = C_1-C_4 hydrocarbyl),[38,39] the *in vitro* pharmacology of which indicates a lack of cholinesterase inhibitory activity,[39] the presence of opioid activity[39] and a receptor profile similar to that of a μ-opioid agonist.[39] A clinical evaluation of these echibolines would be of interest.



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Stimulated by such a catalogue of useful applications, it is therefore not surprising that (-)-physostigmine and its component 1,2,3,3a,8,8a-hexahydro-3a-methylpyrrolo[2,3-*b*]indole ring system has continued to attract considerable synthetic attention.[11,17,36,40,41] However, two early significant synthetic approaches furnished enigmatic results, *a comprehensive interpretation and clarification of which has not, as yet, appeared in the literature* and which is, therefore, the objective of this present study.

Pioneering work toward the synthesis of (-)-physostigmine and its component tricyclic system took the form of concomitant independent investigations by three research groups - one each in the United States of America, in Japan and in Great Britain.

The first successful synthesis of (-)-physostigmine to be reported resulted from some thorough and extremely focused experimentation[42-45] effected under the direction of Percy Lavon[27] Julian in the Chemical Laboratory of DePauw University, Greencastle, Indiana and the aim of which, in tandem with the alkaloid's structural verification, was to develop a facile and economical synthetic route to (-)-physostigmine in excellent yields and in any desired quantity.[43-45] In fact, as recently as 1998 it was stated[27] that "Although there have been more than half a dozen subsequent syntheses of physostigmine, Julian's classical approach, with some recent modifications, is still the best route to the synthetic alkaloid ..."

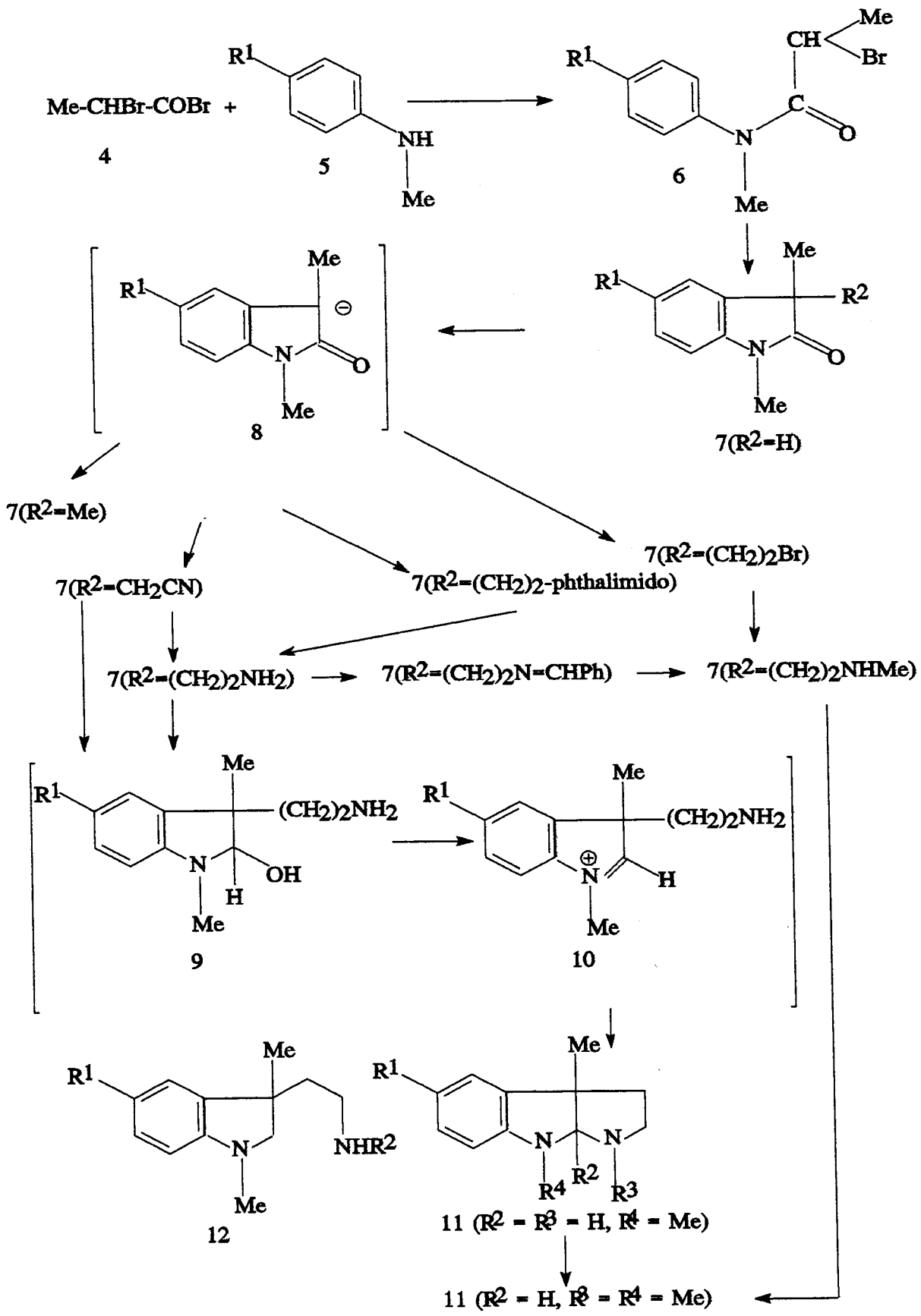
Preliminary exploratory investigations included a synthesis, using the method of Stollé [by reaction of 2-bromopropanoyl bromide (**4**) with *N*-methylaniline (**5**, R^1 = H) to afford the anilide (**6**) (R^1 = H) which was then cyclized by heating with sublimed aluminum chloride (NOTE 4)], of 1,3-dimethylindolin-2-one (**7**, $R^1 = R^2$ = H). This, *via* the *in situ* formation of the intermediate anion (**8**) (R^1 = H) by reaction with sodium ethoxide in dry ethanol, was then subjected to 3-methylation by addition of iodomethane to the ethanolic solution boiling under reflux to give compound (**7**) (R^1 = H, R^2 = Me).[42]

The synthetic objective of the (-)-physostigmine tricyclic ring system was then addressed[42] by substitution with chlorocyanomethane for iodomethane in the 3-alkylation stage of the indolin-2-one (**7**) ($R^1 = R^2$ = H). This afforded, in 90% yield, compound (**7**) (R^1 = H, R^2 = CH_2CN), reduction of which with sodium in boiling (presumably under reflux) dry ethanol effected the simultaneous reduction of both the indolin-2-onic carbonyl group and the cyano group to give the intermediate (**9**) (R^1 = H), acidification of which then forming the intermediate (**10**) (R^1 = H) from which, after intramolecular nucleophilic attack on its imino cationic moiety, (±)-desoxynoreseroline (**11**, R^1-R^3 = H, R^4 = Me) was isolated upon basification.[42] Methylation with iodomethane in dry ether then afforded (±)-desoxyeseroline (**11**, $R^1 = R^2$ = H, $R^3 = R^4$ = Me).[42] However, in this latter approach, "the reduction of a nitrile to an amine with sodium and alcohol does not result generally in good yields"[43] (probably because of competitive alkaline hydrolysis of the cyano group to the corresponding carboxylate as a consequence of the difficulty in excluding moisture from the reaction mixture) and it was therefore replaced, prior to the reductive cyclization, by hydrogenation

over Adams palladium catalyst, to afford **7** (R^1 = H, R^2 = $(CH_2)_2NH_2$).[43] This could also be prepared from 1,3-dimethylindolin-2-one (**7**, R^1 = R^2 = H) by treatment of the sodium salt in dry ethanol with 2-bromoethylphthalimide to yield **7** (R^1 = H, R^2 = $(CH_2)_2$-phthalimido),[43] followed by hydrazinolysis.[43] The isolation of this amine served not only the purpose of improving the yield of the cyclized product but also permitted the obviation of another difficulty, namely the *N*-methylation of (±)-desoxynoreseroline (**11**, R^1 - R^3 = H, R^4 = Me) to (±)-desoxyeseroline (**11**, R^1 = R^2 = H, R^3 = R^4 = Me). Thus, reaction of the amine (**7**) (R^1 = H, R^2 = $(CH_2)_2NH_2$) with benzaldehyde at room temperature readily yielded the benzylidene derivative (**7**) (R^1 = H, R^2 = $(CH_2)_2N$ = CHPh) which was subsequently almost quantitatively quaternized by heating with iodomethane in a sealed tube at 100 °C, followed by hydrolysis to afford **7** (R^1 = H, R^2 = $(CH_2)_2NHMe$).[43] This was reductively cyclized using sodium in "absolute alcohol" (anhydrous ethanol) (NOTE 5) to yield (±)-desoxyeseroline (**11**, R^1 = R^2 = H, R^3 = R^4 = Me).[43]

However, since it had been already established that by catalytic hydrogenation,[8] as well as by reduction with zinc and hydrochloric acid,[46] eserethole (**11**, R^1 = EtO, R^2 = H, R^3 = R^4 = Me) is smoothly converted into compound (**12**) (R^1 = EtO, R^2 = Me) (NOTE 6), it was considered possible that nascent hydrogen in an alkaline medium might effect a similar reduction and that as a result the final products resulting from these above syntheses might be **12** (R^1 = H, R^2 = H and Me, respectively).[43] However, the latter possible structures, which "could not be excluded satisfactorily solely on the basis of analytical figures",[43] were duly eliminated when it was shown that the final products from these syntheses had properties characteristic of secondary and tertiary amines, respectively,[43] and, like eserethole (**11**, R^1 = EtO, R^2 = H, R^3 = R^4 = Me), both were reductively cleaved, catalytically, to yield 2,3-dihydrotryptamines - in their cases **12** (R^1 = H, R^2 = H and Me, respectively)[43] - and other parallel chemical reactivities were noted.[43] The scene, therefore, was set for a synthesis of (-)-physostigmine by the following route:-[44,45]

2-Bromopropanoyl bromide (**4**) was reacted with *N*-methyl-*p*-phenetidine (**5**, R^1 = EtO) to yield the anilide (**6**) (R^1 = EtO) which, upon heating with an excess of sublimed aluminum chloride (NOTE 4), underwent cyclization and cleavage of the ethoxy bond to afford, in excellent yield, 1,3-dimethyl-5- hydroxyindolin-2-one (**7**, R^1 = HO, R^2 = H).[44] After reethylation of the 5-hydroxyl group by treatment in 5% potassium hydroxide solution with diethyl sulfate, the resulting product (**7**) (R^1 = EtO, R^2 = H) was 3-alkylated using chlorocyanomethane to give **7** (R^1 = EtO, R^2 = CH_2CN) (NOTE 7). Hydrogenation over Adams palladium catalyst then yielded **7** (R^1 = EtO, R^2 =


Me-CHBr-COBr +
4
5
6
7(R2=H)
8
7(R2=Me)
7(R2=CH2CN)
7(R2=(CH2)2-phthalimido)
7(R2=(CH2)2Br)
7(R2=(CH2)2NH2)
7(R2=(CH2)2N=CHPh)
7(R2=(CH2)2NHMe)
9
10
12
11 (R2 = R3 = H, R4 = Me)
11 (R2 = H, R3 = R4 = Me)

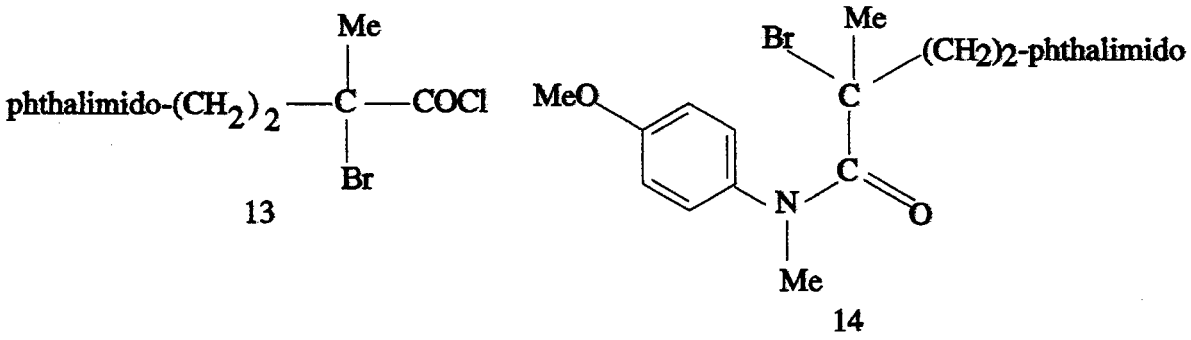
$(CH_2)_2NH_2$).[44] Condensation of this with benzaldehyde - to give **7** (R^1 = EtO, R^2 = $(CH_2)_2N$ = CHPh) - followed by quaternization with iodomethane and then hydrolysis effected conversion into **7** (R^1 = EtO, R_2 = $(CH_2)_2NHMe$).[44] This could also be prepared by heating with methanolic methylamine at 100 °C the product (**7**) (R^1 = EtO, R^2 = $(CH_2)_2Br$) that results from the treatment of 1,3-dimethyl-5-ethoxyindolin-2-one (**7**, R^1 = EtO, R^2 = H), as its sodium salt, with1,2-dibromoethane.[43,45] Reductive cyclization of compound (**7**) (R^1 = EtO, R^2 = $(CH_2)_2NHMe$) using sodium in "absolute alcohol" (NOTE 5) then afforded (±)-eserethole (**11**, R^1 = EtO, R^2 = H, R_3 = R_4 = Me) to complete a synthetic sequence whose yields at every stage are excellent.[44]

However, attempts to optically resolve (NOTE 8) the (±)-eserethole using either (+)-camphorsulfonic acid or (+)-tartaric acid were unsuccessful.[45] Nevertheless, by the successive reaction with these acids, the amine **7** (R^1 = EtO, R_2 = $(CH_2)_2NHMe$) was resolved, in excellent yields, into its (+)- and (-)- enantiomers,[45] the latter of which underwent reductive cyclization to yield (-)-eserethole.[45] This, by boiling under reflux its solution in petroleum ether (bp 70-77 °C) in which anhydrous aluminum chloride was suspended, was smoothly converted into (-)-eseroline (**2**, R = H, X = NMe).[45] Since this product had already been converted into (-)-physostigmine (**2**, R = MeNH-CO, X = NMe)[47] by reaction of its anhydrous ethereal solution containing a trace of sodium with methylisocyanate in benzene, a *first* total synthesis of the alkaloid had therefore been achieved.

It is poignant to note that the funding of this research appears to reflect then current social attitudes prevalent in the United States of America in that the concluding paragraph of the final paper announcing the development of the synthesis reads "In acknowledging a generous grant from the Rosenwald Fund, the senior author respectfully dedicates this finished project to the memory of Julius Rosenwald, who has made possible innumerable cultural contributions on the part of young negroes to his country's civilization."[45] Indeed, when the present author had the pleasure of meeting with him in Chicago on 22nd June 1972, it became apparent that Dr. Julian, as a result of his being an Afro-American (he was the grandson of a slave, and had been born in Montgomery, Alabama in 1899[27]), had, during the early period of his life, for many years experienced and been the victim of the racial segregation that was then practised within the United States of America.

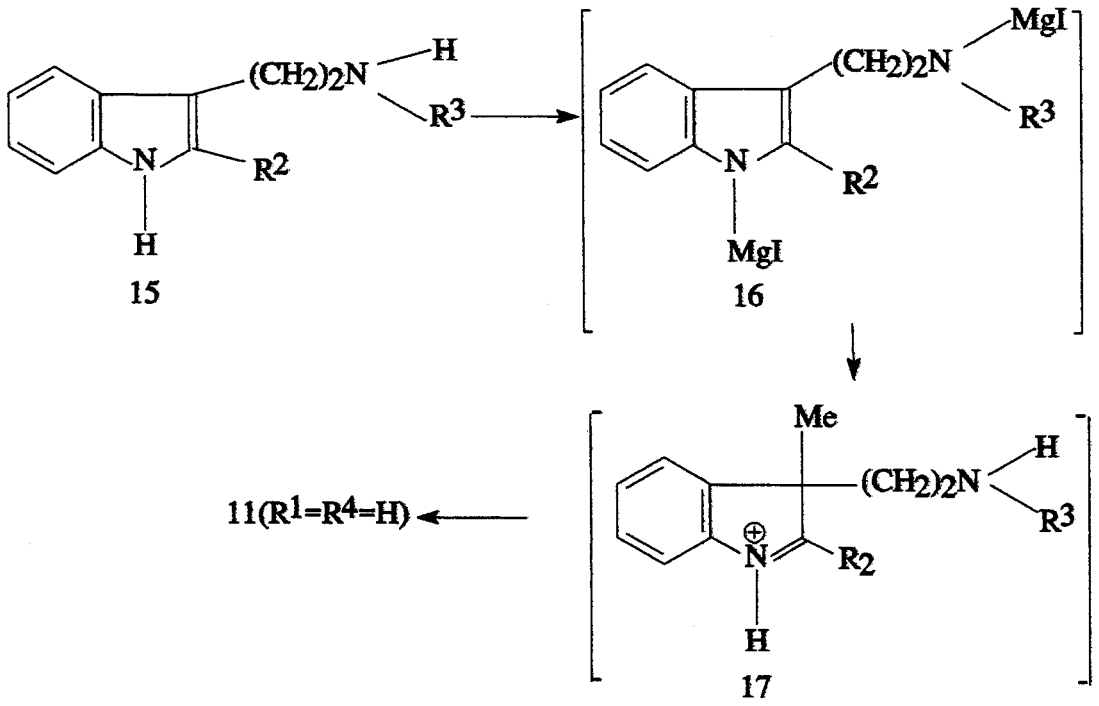
Synthetic studies, apparently initiated concomitantly with but not reported until some *twenty-five years later*[48] than those of Julian, independently followed the latter's route but with an interesting variation on the approach of Stollé to the necessary

indolin-2-onic intermediate.[48] Thus, 2-bromo-2-methyl-4-phthalimidobutanoyl chloride (**13**) was reacted with *N*-methyl-*p*-anisidine (**5**, R^1 = MeO) to afford the anisidide (**14**) which was cyclized by fusion with a (5:1 $^{w}/_{w}$) mixture of aluminum chloride with sodium chloride (NOTE 4). These conditions also effected *O*-demethylation to yield the indolin-2-one (**7**) (R^1 = HO, R^2 = $(CH_2)_2$-phthalimido) that was then sequentially *O*-methylated with diazomethane and subjected to hydrazinolysis to give **7** (R^1 = MeO, R^2 = $(CH_2)_2NH_2$). This, following a route analogous to that reported by Julian, namely, *N*-methylation *via* quaternization with iodomethane and then hydrolysis of the benzylidene derivative followed by reductive cyclization using sodium in ethanol, gave (±)-esermethole (**11**, R^1 = MeO, R^2 = H, R^3 = R^4 = Me).[48]

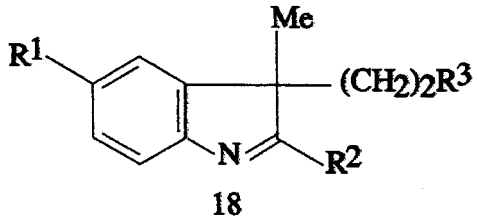


Almost at the same time as Julian and Pikl, and with the same synthetic objective, Hoshino and Kobayashi, with their occasional co-workers, in Japan developed a scheme in which tryptamines, with both N-atoms at least secondary **15**, were subjected to 3-methylation *via* sequential formation, by reaction with either ethyl- or methylmagnesium iodide, of their adducts (**16**) followed by reaction with iodomethane in anhydrous ether, anisole or benzene boiling under reflux. Work-up by hydrolysis with acid then afforded the 3*H*-indolium cation (**17**), the imonium function of which, as in Julian and Pikl's synthesis, readily undergoes intramolecular nucleophilic attack, with subsequent basification yielding the corresponding 1,2,3,3a,8,8a-hexahydro-3a-methylpyrrolo[2,3-*b*]indoles, including, for example, compounds (**11**) (R^1 - R^4 = H),[49-51] (R^1 = R^3 = R^4 = H, R^2 = Me),[49-51] (R^1 = R^2 = R^4 = H, R^3 = Me),[52] (R^1 = MeO, R^2 - R^4 = H),[53] (R^1 = EtO, R^2 - R^4 = H)[53] and (R^1 = EtO, R^2 = R^4 = H, R^3 = Me).[52,54]

In an extension to this synthetic approach,[55] 3-methylindole, 2,3-dimethylindole and 5-ethoxy-3-methylindole were reacted sequentially with ethylmagnesium iodide in ether and then with 1,2-dibromoethane to yield the 3*H*-indoles (**18**) (R^1 = R^2 = H, R^3 = Br; R^1 = H, R^2 = Me, R^3 = Br and R^1 = EtO, R^2 = H, R^3 = Br, respectively). These, upon heating with ethanolic ammonia at 100-105 °C for 16 h, were converted into **11** (R^1 - R^4 = H; R^1 = R^3 = R^4 = H, R^2 = Me and R^1 = EtO, R^2 - R^4 = H, respectively), with



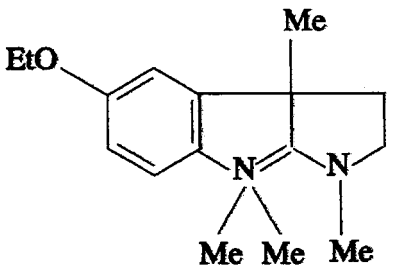
compound (**18**) (R^1 = EtO, R^2 = H, R^3 = Br) being similarly converted into **11** (R^1 = EtO, R^2 = R^4 = H, R^3 = Me) by heating with "alcoholic" methylamine at 100-105 °C for 15 h.[55]



In order to advance these above studies toward the synthetic objective of (-)-physostigmine, a series of investigative *N*-methylations of their final products were effected. As a result of these it was established that (±)-isonoreserethole (**11**, R^1 = EtO, R^2 = R^4 = H, R^3 = Me),[52,54] as its hydrochloride, when heated with iodomethane in methanol yields (±)-eserethole (**11**, R^1 = EtO, R^2 = H, R^3 = R^4 = Me)[56] which, *via* the formation of its salt with either (-)- or (+)- tartaric acid, could - contrary to the earlier observation of Julian and Pikl[45] (*vide supra*) - be optically resolved.[56] Then, application of already-published procedures[45] involving *O*-deethylation of the (-)- and (+)-enantiomers and the racemate by heating with anhydrous aluminum chloride suspended in petroleum ether gave (-)-, (+)- and (±)-eserolines[45] which, upon treatment in anhydrous ether with a trace of sodium followed by methyl isocyanate in benzene[47] resulted in a *second* successful total synthesis of (-)-physostigmine (**2**, R = MeNH-CO, X = NMe) along with those of its enantiomer and its racemate.[56] However,

the salicylates of the enantiomers are quoted[56] as being dextrorotatory and laevorotatory, respectively, which is contrary to now well-established data[28] and thus it has been concluded[28] that this work "leaves much to be desired".

Another *N*-methylation of particular significance (*vide infra*) involved that by various procedures of (±)-dinoreserethole (**11**, R^1 = EtO, R^2 - R^4 = H), reactions from which a base was isolated. This was assigned[57] a molecular formula $C_{16}H_{24}N_2O$ and three *N*-methyl groups, was ultimately to be designated "methyl-eserethole", and was given the structure (**19**).[57] However, it was later appreciated that "This is a highly improbable



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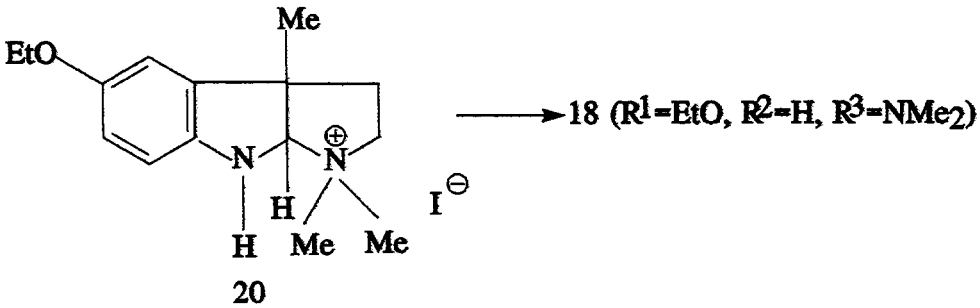
constitution"[58] - and indeed, that it "cannot be correct since it violates fundamental theory",[59] although it has been regurgitated without comment.[44] Moreover, concomitantly with further methylations - mostly effected with iodomethane under effectively either neutral or alkaline conditions - of (±)-dinoreserethole (**11**, R^1 = EtO, R^2 - R^4 = H) and (±)-isonoreserethole (**11**, R^1 = EtO, R^2 = R^4 = H, R^3 = Me) to give "methyl-eserethole",[56] its molecular formula was revised to $C_{15}H_{22}N_2O$ and it was found to contain only two *N*-methyl groups,[56] conclusions that were later confirmed (NOTE 9) by Robert Robinson's group in Oxford. Also of considerable significance was the reaction of (±)-isonoreserethole methiodide (**20**) with cold dilute alkali to afford an



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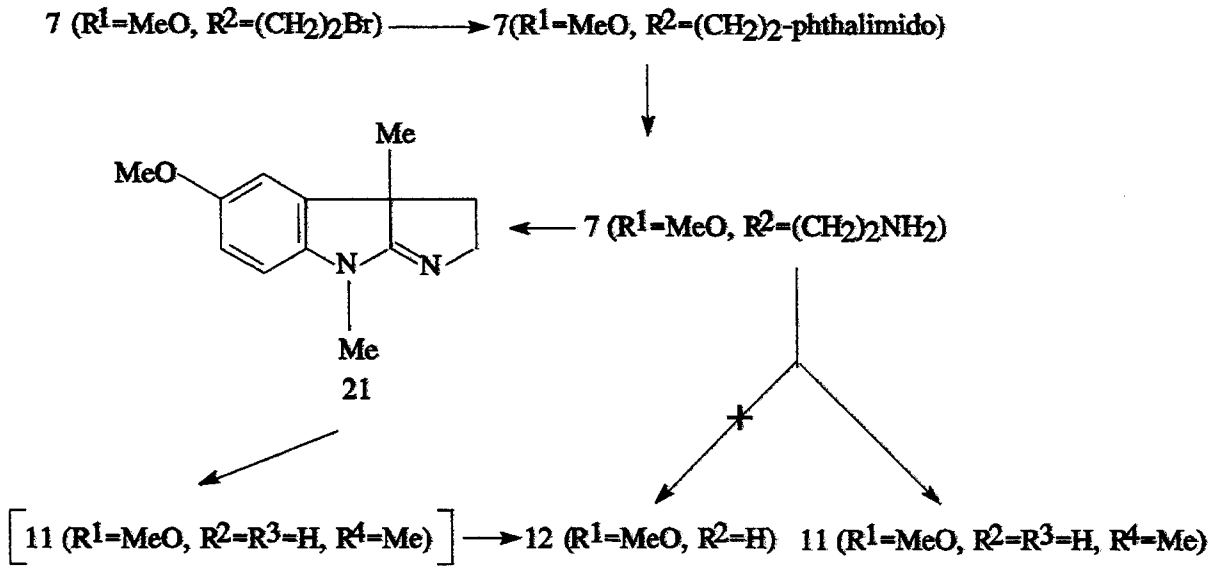
almost quantitative yield of "methyl-eserethole", an observation fromwhich it follows that "methyl-eserethole" has structure (**18**) (R^1 = EtO, R^2 = H. R^3 = NMe_2).[56] This postulation was ultimately verified[55] by synthesis involving the sequential reaction of 5-ethoxy-3-methylindole with ethylmagnesium iodide in anhydrous ether and then with

1,2-dibromoethane to yield the 3*H*-indole (**18**) (R^1 = EtO, R^2 = H, R^3 = Br) which, upon heating with alcoholic dimethylamine affords "methyl- eserethole".[55]

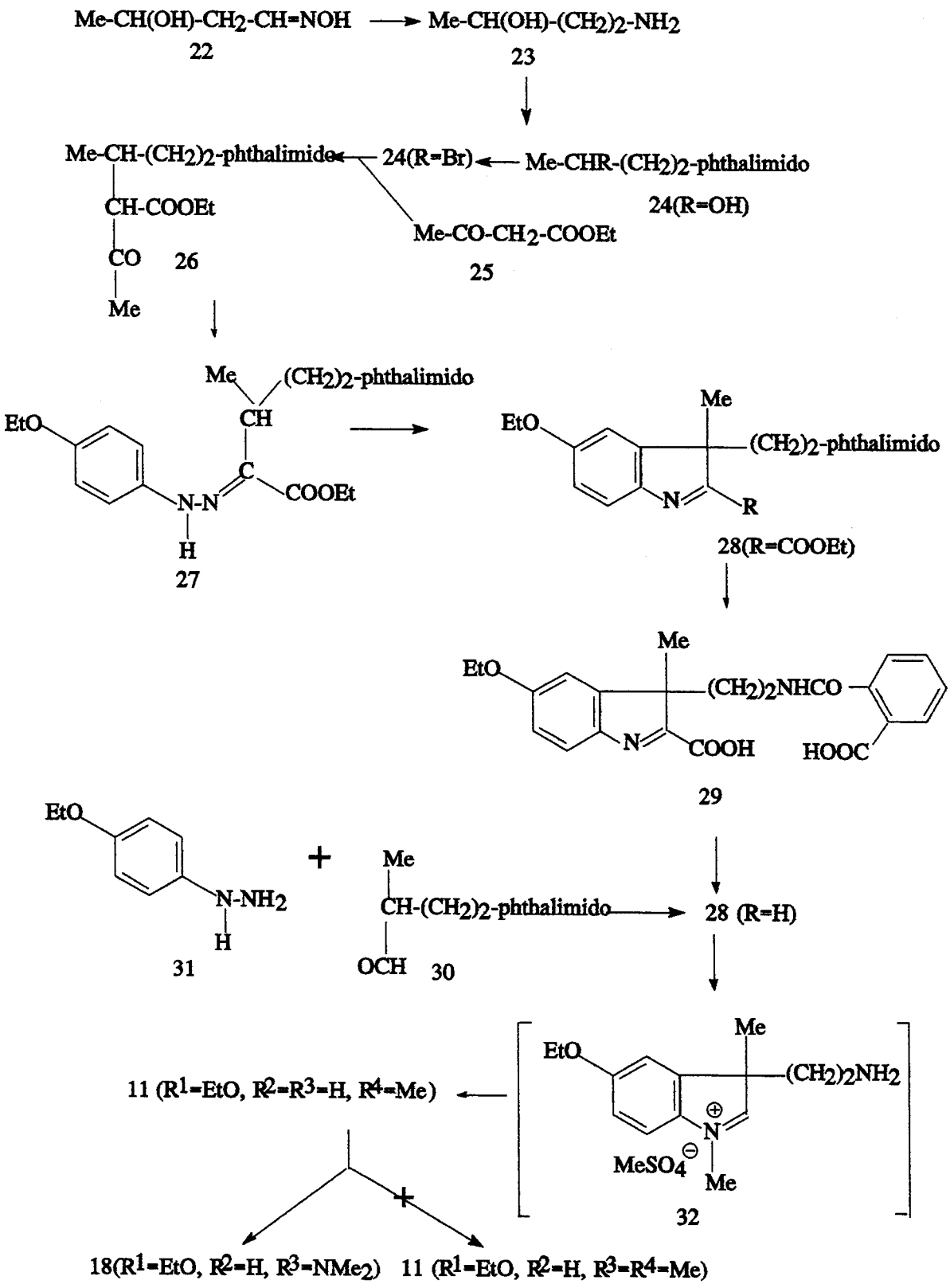
The third group whose synthetic sights were focused upon (-)-physostigmine during the 1930s was that directed by Robert Robinson - initially at the University of Manchester[60,61] and later at the Dyson Perrins Laboratory in the University of Oxford -and the work of which was reported in a short series of closely inter-related, and consequently somewhat fragmented and reiterative, papers, the clarity of which thus occasionally leaves much to be desired. Nevertheless, they do constitute the first published approach toward (-)-physostigmine's synthesis although, unfortunately, without ultimate success (NOTE 9). So where, why and how did these synthetic efforts break down? Sometimes this group either missed or failed to reach its synthetic destination and, indeed, failed to realize in one instance that it had arrived!

This situation arose in connection with a reaction sequence that involved the intermediacy of the unequivocally-synthesized compound (**7**) (R^1 = MeO, R^2 = $(CH_2)_2Br$).[62] This, upon reaction with potassium phthalimide, afforded **7** (R^1 = MeO, R^2 = $(CH_2)_2$phthalimido)[63] which upon hydrazinolysis gave **7** (R^1 = MeO, R^2 = $(CH_2)_2NH_2$).[63] The pyrrolo ring was then formed by reaction with phosphorus pentoxide in dry xylene boiling under reflux to afford the cyclic amidine (**21**).[63] This was then reduced by hydrogenation in the presence of a platinum catalyst in ethyl acetate (no more precise conditions were stated) to give a product that was thought to be **11** (R^1 = MeO, R^2 = R^3 = H, R^4 = Me)[63] (characterized as its picrolonate[63]) and which was then *N*-methylated to yield what was claimed[58] to be (±)-esermethole (NOTE 10). However, it would appear that the conditions employed for the reduction of the cyclic amidine (**21**) do not preclude the reductive cleavage of the tetrahydropyrrolo ring C in the now-believed to be the intermediately-formed compound (**11**) (R^1 = MeO, R^2 = R^3 = H, R^4 = Me) (NOTE 6) and there is every reason to suppose that the reduction as effected by Robert Robinson's group continues right though to the 2,3-dihydrotryptamine (**12**) (R^1 = MeO, R^2 = H).[59,64,65] In his failure to appreciate this possibility, Robert Robinson was clearly less prudent than had been Percy Julian[43] (*vide supra*). Indeed, it was later recognized[59] that it was this shortcoming that led the Oxford group astray in the identification of the product resulting from its reduction of compound (**7**) (R^1 = MeO, R^2 = $(CH_2)_2NH_2$) - which they synthesized as described above[63] - using sodium in boiling (presumably under reflux) *iso*amyl alcohol.[63] By analogy with the subsequent work of Julian and Pikl (*vide supra*), this reaction could only have given (±)-noresermethole (**11**, R^1 = MeO, R^2 = R^3 = H, R^4 = Me) (NOTE 11) but the contemporary suggestion[63] was that, since the product was, by comparison of its picrolonate,

different from that produced by the reduction of the cyclic amidine (**21**) - which was then thought to have yielded **11** (R^1 = MeO, R^2 = R^3 = H, R^4 = Me) - it had afforded **12** (R^1 = MeO, R^2 = H)[63] (NOTE 9). *Thus it would appear "that the actual structures"[59] of the products resulting from the reductions of the cyclic amidine (**21**) and the indolin-2-one (**7**) (R^1 = MeO, R^2 = $(CH_2)_2NH_2$) "are in fact the reverse of those originally assigned by King and Robinson".*[59]

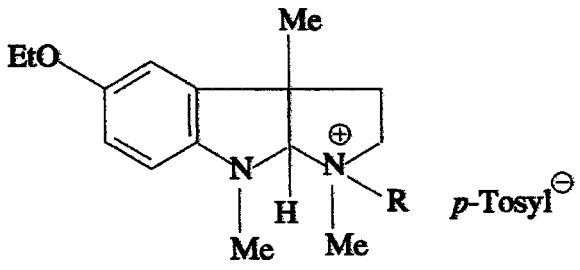


In addition to the above studies, Robert Robinson and his team also developed a further potential - but again unsuccessful - route toward a synthesis of (-)-physostigmine, now starting from acetaldoloxime (**22**). This was reduced by aluminum amalgam in water into 3-hydroxybutylamine (**23**) which, when heated with phthalic anhydride, gave **24** (R = OH).[61] Reaction of this with hydrogen bromide in ethanol afforded **24** (R = Br) which upon treatment with ethyl acetoacetate (**25**) in the presence of ethanolic potassium ethoxide led to **26** which, when coupled with 4-ethoxybenzenediazonium chloride in alkaline solution, lost an acetyl group and gave the arylhydrazone (**27**).[61] Fischer cyclization[41] of this by reaction in boiling ethanolic hydrogen chloride under reflux then yielded the 3*H*-indole (**28**) (R = COOEt).[61] This, upon hydrolysis with ethanolic potassium hydroxide, afforded **29** which was decarboxylated and dehydrated by boiling in xylene under reflux to afford **28** (R = H).[61,66] However, because of competing side-reactions,[61] the yield from this latter reaction was very low (6.6-8.5%)[61] but this shortcoming was obviated by the direct preparation of **28** (R = H) *via* the Fischer indolization[41] of a mixture of the aldehyde (**30**), that was synthesized using standard procedures,[58,67] with 4-ethoxyphenylhydrazine (**31**) in saturated "alcoholic" hydrogen chloride.[67] The protecting phthaloyl group was then removed from the methosulfate of compound (**28**) (R = H), usinghydrazine hydrate in boiling "alcohol" (under reflux?) followed by


Me-CH(OH)-CH2-CH=NOH
22
Me-CH(OH)-(CH2)2-NH2
23
Me-CH-(CH2)2-phthalimide
CH-COOEt
CO
Me
26
24(R=Br)
Me-CHR-(CH2)2-phthalimido
24(R=OH)
Me-CO-CH2-COOEt
25
Me
(CH2)2-phthalimido
CH
C
COOEt
EtO
N-N
H
27
Me
EtO
(CH2)2-phthalimido
N
R
28(R=COOEt)
Me
EtO
(CH2)2NHCO
N
COOH
HOOC
29
EtO
N-NH2
H
31
+
Me
CH-(CH2)2-phthalimido
OCH
30
28 (R=H)
11 (R1=EtO, R2=R3=H, R4=Me)
Me
EtO
(CH2)2NH2
N
MeSO4
Me
32
+
18(R1=EtO, R2=H, R3=NMe2)
11 (R1=EtO, R2=H, R3=R4=Me)

acidification with hydrochloric acid, toafford, *via* the intermediacy of **32**, and after basification, (±)-noreserethole (**11**, R^1 = EtO, R^2 = R^3 = H, R^4 = Me)[61] (NOTE 9) [(±)-noresermethole (**11**, R^1 = MeO, R^2 = R^3 = H, R^4 = Me) was also similarly prepared[58]]. The methylation of the former product using methyl *p*-toluenesulfonate was claimed by Robert Robinson and his co-workers[58,66,68] to give (±)-eserethole (**11**, R^1 = EtO, R^2 = H, R^3 = R^4 = Me). However, this was not so (NOTE 9) and it was at this final stage that this synthetic effort broke down to afford as product "methyl-eserethole" (**18**, R^1 = EtO, R^2 = H, R^3 = NMe_2) (NOTE 9). So once again the Oxford group's endeavors had been thwarted by a cleavage of the tetrahydropyrrolo ring of the 1,2,3,3a,8,8a-hexahydro-3amethylpyrrolo[2,3-*b*]indole moiety.

Although the formation of "methyl-eserethole" from the methylation of either (±)-dinoreserethole (**11**, R^1 = EtO, R^2 - R^4 = H)[57] or (±)-isonoreserethole (**11**, R^1 = EtO, R^2 = R^4 = H, R^3 = Me)[56] (*vide supra*) is without problem since it clearly occurs *via* a simple dimethylation of the N_1-atom,[59] its formation from Robert Robinson's methylation of (±)-noreserethole (**11**, R^1 = EtO, R^2 = R^3 = H, R^4 = Me),[58,66,68] involving as it does the loss of a methyl group from N_8, is far from clear but has been subjected to considerable speculation and experimentation.[59] Although it was thought to be unlikely, the possibility that the methyl *p*-toluenesulfonate used by the Oxford group in their alkylation of (±)-noreserethole (**11**, R^1 = EtO, R^2 = R^3 = H, R^4 = Me)[58,66,68] first afforded



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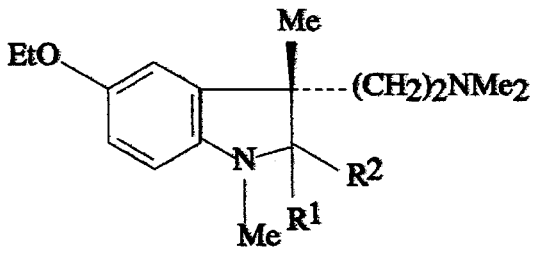
(±)-eserethole *p*-toluenesulfonate (**33**, R = H) which then rearranged into "methyl-eserethole" (**18**, R^1 = EtO, R^2 = H, R^3 = NMe_2) was investigated, and apparently eliminated, when compound (**33**) (R = H), formed by treating (±)-eserethole (**11**, R^1 = EtO, R^2 = H, R^3 = R^4 = Me) with one equivalent of *p*-toluenesulfonic acid, after exposure to the same conditions as were employed for the methylation of (±)-noreserethole[58,66,68] led to an almost quantitative recovery of unchanged (±)-eserethole as the only product.[59] However, another remaining possibility is that the methyl *p*-toluenesulfonate effects a dimethylation of N_1, the much more basic nitrogen atom, to give compound (**33**) (R = Me) which upon basification would afford (±)-eserethole methine (racemic **34**, R^1 = OH, R^2 = H) that, as in the work of Robert Robinson's group,

would be readily extracted into ether and could, not inconceivably, upon distillation simply lose methanol to afford "methyl-eserethole" (**18**, R^1 = EtO, R^2 = H, R^3 = NMe_2),[59] the crucial point being not only the Oxford group's product distillation but also the



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latter's conditions. In an attempt to verify this theory, eserethole methine (**34**, R^1 = OH, R^2 = H) was prepared from (-)-physostigmineas already reported[46] and subjected to distillation at various temperatures.[59] At temperatures of below 120 °C and pressures of the order of 0.1 mm or less it distilled unchanged whereas at higher temperatures decomposition slowly occurred and, by fractional crystallization of their picrates, the distillate afforded the picrate of dehydroeserethole methine (**34**, R^1 + R^2 = O), prepared by alkaline ferricyanide oxidation of eserethole methine (**34**, R^1 = OH, R^2 = H),[8] and the methopicrate of eserethole - resulting from unchanged eserethole methine.[59] Since it appears that the former product may have resulted from aerial oxidation of the eserethole methine, this latter was therefore heated at 170 °C for 3 h under an atmosphere of nitrogen and then distilled at 0.1 mm, but the only product was impure eserethole methine, isolated as eserethole methopicrate from the distillate.[59] In view of the failure to detect from any of the above experiments any "methyl-eserethole" it was therefore concluded that its formation "on methylation of noreserethole thus still remains something of a mystery, though the author's explanation is regarded as at least a partial solution of the problem."[59] However, further experimental investigation is required in order to clarify this situation.

NOTES

1. However, the plant's habitat is much wider than this might suggest for it has been reported[69] that it is distributed throughout West Africa from Sierra Leone to the Congo. Nevertheless, in spite of it being so widespread, the plant is rather rare and is of erratic local occurrence because, in its efforts to eliminate the use of the Calabar bean as an ordeal poison, the former British colonial government prohibited the parent plant's cultivation and exterminated as far as possible existing species[69] although, when it was recently stated that the West African habitat of *P. venenosum* was "near mouths of Niger and Old Calabar Rivers" it was also noted that it has been

"introduced into India and Brazil".[70]

2. Other natural sources have also been reported for (-)-physostigmine which occurs in *P. cylindrospermum* Holmes (seeds) (family Leguminosae),[71] *P. mesoponticum* seeds (family Leguminosae),[74] *Vicia calabarica* (family Leguminosae),[75] *Mucuna urens* Medic and *M. cylindrosperma* Welw. ex Baker (family Leguminosae),[76] various *Dioclea* species[77] (all of which, being climbers and bearing fruit in long pods,[77] are legumes) – notably *D. microcarpa* Huber,[77,78] but also allegedly in *D. bicolor*,[78] *D. lasiocarpa*,[78] *D. reflexa*[78] and *D. violacea*,[78] and, allegedly but without unequivocal characterization, in the fresh ripe fruit of *Hippomane mancinella* that closely resemble crab apples in size and color and which were harvested from trees near Bear Lake in the Everglades National Park, Homestead, Florida, in the United States of America.[79] Furthermore, it is the first example of an alkaloid (plant-derived) that has also been obtained from a microorganism when it was found to be produced by *Streptomyces* sp. AH-4[21] and by *S. pseudogriseolus*.[20,80] Indeed, such microbial production opens the way for its production by fermentation, a useful alternative to its extraction from the ripe seeds of *P. venenosum* which are only harvested in tropical areas and may, in addition, often be only sparingly available because of local legislation prohibiting the cultivation of and, moreover, ordering the destruction of their parent plant (NOTE 1).

3. Such antiamnesic activity may also be manifest in one of the minor alkaloids of *P. venenosum*, (-)-physovenine (**2**, R = MeNH-CO, X = O),[7,36,81-83] that is, like (-)-physostigmine (**2**, R = MeNH-CO, X - NMe), a highly active inhibitor of acetylcholinesterase[84] but may be more lipophilic - with a consequent increased ability to cross the blood-brain barrier - than the latter alkaloid (although this, being a tertiary amine, can penetrate this barrier,[15] unlike, for example, neostigmine, its synthetic analogue but a quaternary ammonium ion[17]).

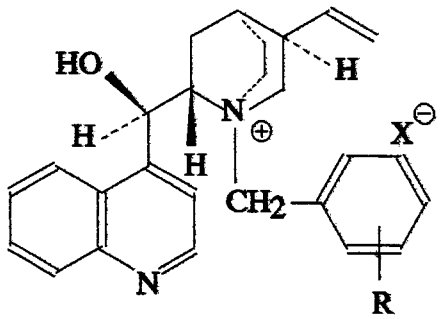
4. If, instead of using aluminum chloride alone, a melt of a mixture of aluminum chloride with sodium chloride (5:1 $^{w}/_{w}$) is employed to effect this type of cyclization, the resulting yields of product may be substantially increased.[48]

Alternatively, the Stollé approach to the required indolin-2-onic synthetic intermediate could be replaced by the Brunner synthesis.[41] Indeed, this is a method of choice for the preparation of 3-alkylindolin-2-ones - affording yields in the region of up to 80%[41] and, furthermore, its use would circumvent the undesired *O*-dealkylation[44,48] and thereby obviate the necessity of the *O*-realkylation stage.[44,48]

5. The reductive cyclization of, for example, **7** (R^1 = H, R^2 = $(CH_2)_2NH_2$) into **11** (R^1 – R^3 = H, R^4 = Me) using sodium in "alcohol" requires large amounts of sodium and "alcohol". This consequently makes the experimental procedure cumbersome and labor-intensive, disadvantages that were later ameliorated by the introduction of lithium aluminum hydride, in either "dioxane" or "tetrahydrofuran", as the reducing agent,[85,86] conditions that can also be employed in the direct reductive cyclization of the Julian nitriles (**7**) (R^2 = CH_2CN).[31,85,87]

6. Contrary to the earlier implication[8] that these reductions, involving zinc and hydrochloric acid[46] and hydrogenation over platinum in glacial acetic acid,[8] must have involved the direct rupture of the C_{8a}-N_1 bond, which "seems rather unlikely as this is not activated, *e.g.* benzylically or allylically,"[88] it has been suggested that they occur *via* an acid-catalysed ring-C cleavage of **11** to afford a 3*H*-indolium cation such as **10** and that it is the imonium function thus formed that is reduced.[88] Verification for this arises from the observation that "no reduction occurs in neutral or alkaline solution."[88] Thus the 1,2,3,3a,8,8a-hexahydro-3a-methylpyrrolo[2,3-*b*]indole ring system is unaffected under conditions of hydrogenation over a palladium-on-carbon catalyst in methanol[31,89] and it also explains why the C_{8a}-N_1 bond in Julian and Pikl's product is stable to sodium in boiling dry ethanol under reflux.

7. Alkylations such as this can now be effected asymmetrically by phase-transfer catalysis using chiral catalysts. For example, with **7** (R^1 = MeO, R^2 = H) in the presence of **35** (R = 4-CF_3, X = Br; R = 3,4-Cl_2, X = Br and R = 3,4-Cl_2, X = Cl) under phase-transfer conditions, enantiomeric excesses of the *S*-enantiomer of 72%, 77% and 78%, respectively, were realized.[90]



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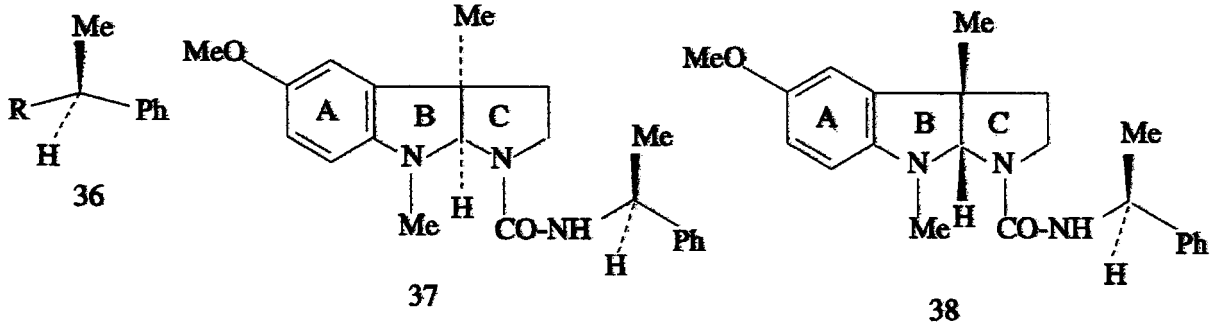
8. The resolution of racemic amines *via* their reaction with an optically active acid to afford a mixture of two diastereoisomeric salts that are then separated by fractional crystallization and from which the optically active amines are subsequently liberated is a widely-employed classical technique. However, sometimes it is either

unsuccessful or proves to be difficult and not very practical, with tedious recrystallizations of the salts being required to yield optically pure materials in consequent low yields. Indeed, such is the case with the resolution of (±)-noresermethole (**11**, R^1 = MeO, R^2 = R^3 = H, R^4 = Me) and (±)-eserethole (**11**, R^1 = EtO, R^2 = H, R^3 = R^4 = Me) which can be separated into their optically pure stereoisomers in only low yields.[91,92] However, an alternative method is now available by which the optically active amines can be obtained from their racemates in high yield and of excellent optical purity. It is similar in principle to the earlier classical method of resolution, involving the preparation of a mixture of two diastereoisomeric derivatives (but in this case ureas, obtained by reacting enantiomeric secondary amines with optically pure isocyanates), their separation (in this instance chromatographically), and finally the liberation of the optically pure amines. This technique is applicable to the resolution of a wide range of racemic secondary amines including, for example,[30,31,91,93] (see also ref 94) that of (±)-N_1-noresermethole (**11**, R^1 = MeO, R^2 = R^3 = H, R^4 = Me) in which a stirred solution of the latter in chloroform at 0 °C is treated by the dropwise addition of the isocyanate (**36**) (R = O = C = N) and, after 2 h, the solvent is evaporated to leave a mixture of the diastereoisomeric ureas **37** and **38** (a discussion of the stereochemistry of the B/C ring junction in the 1,2,3,3a,8,8a-hexahydro-3a-methylpyrrolo[2,3-*b*]indole ring system is presented in NOTE 12). These are then separated by column chromatography[30,93,95] [silica gel/CH_2Cl_2-MeOH (100:1 to 80:1)] and then decomposed by boiling , under reflux and an atmosphere of nitrogen for 2 h,[91-93,95] with either 1M sodium pentoxide in "pentanol" or sodium butoxide in "butanol", or in boiling pentan-l-ol or butan-l-ol alone under reflux,[30,91] to afford the component optical isomers of the (±)-N_1-noresermethole (**11**, R^1 = MeO, R^2 = R^3 = H, R^4 = Me) of excellent optical purity and in high yields [besides **36** (R = $Me(CH_2)_4O$-CO-NH



and $Me(CH_2)_3O$-CO-NH, respectively) which can be reconverted into **36** (R=O=C=N) by hydrolysis to afford **36** (R = NH_2) and then reaction of this with phosgene].[91]

9. In the communication[44] announcing their synthesis of (±)-eserethole, the validity

of which is beyond any doubt, Julian and Pikl state that "In a series of ten beautiful papers Robinson and his co-workers have described syntheses of compounds which they call "*d,l*-eserethole" and "*d,l*-esermethole." Their "*d,l*-eserethole" is not the compound ..... described in this communication as *d,l*-eserethole, and the constitution of which can hardly be questioned. We believe that the English authors are in error, that the compound they describe as *d,l*-eserethole is not the substance, and that we are describing for the first time the real *d,l*-eserethole",[44] and summarise that "The "*d,l*-eserethole" described by other workers in this field is thought to have another constitution than that ascribed to it."[44] They furthermore repeat this conclusion by the comment that "our product was the real *d,l*-eserethole and that that of the English chemists must be assigned another constitution." in their communication concerning their complete synthesis of (-)-physostigmine.[45]

It was, however, recognized by Julian and Pikl that Robert Robinson's synthetic approach was intact until its final stage when they noted[44] that "The English authors depend upon methylation of their *d,l*-noreserethole (which seems to be identical with our product .....) with methyl *p*-toluenesulfonate and at times methyl sulfate. This could well lead to a substance whose structure is represented by [**19**]. A substance with this formula assigned to it has been obtained by Hoshino and Kobayashi through methylation by various procedures of dinoreserethole [*vide supra*]. Its melting point appears to be identical with the "*d,l*-eserethole" of Robinson and his co-workers and likewise the melting points of the two picrates seem identical."[44] Indeed, such was reported[68] as being corroborated "by a direct comparison of the specimens", at which juncture the molecular formula of "methyl-eserethole" was also confirmed as $C_{15}H_{22}N_2O$ which contained only two *N*-methyl groups[68] - ultimately it was shown to have structure (**18**) (R^1 = EtO, R^2 = H, R^3 = NMe_2) (*vide supra*). Nevertheless, the Oxford group tenaciously refused to accept the unequivocal fact that their synthesis had collapsed at this stage by their statement that "In our opinion the base is structurally identical with eserethole, and it may be a stereoisomeride of this base [NOTE 12]. We accept the evidence of Hoshino and Kobayashi (*loc. cit.*) that the substance is not *d,l*-eserethole, although the facts leading to this conclusion have not fallen within our experience,"[68] However, Robert Robinson and his group at Oxford were *never to reach their synthetic objective of (-)-PHYSOSTIGMINE*. Indeed, this was further manifest by their failure to prepare (±)-noresermethole (**11**, R^1 = MeO, R^2 = R^3 = H, R^4 = Me) by heating 5-methoxy-1,3-dimethylindole with an excess of ethyleneimine in a sealed tube at 120 °C for 3 h which, perhaps not surprisingly, afforded only unchanged indolic starting material.[96]

10. This claim was later shown to be erroneous since the product gave a picrate, small yellow prisms from "alcohol", mp 180-181 °C[58] which is clearly different from the picrate - orange crystals from "alcohol", mp 150 °C[64] (a later observation reported orange-yellow dice from ethanol, mp 162-163 °C[48]) - of (±)-esermethole (**11**, R^1 = MeO, R^2 = H, R^3 = R^4 = Me) that was independently and unequivocally synthesized using Julian and Pikl's approach involving as the final step the reductive cyclization of **7** (R^1 = MeO, R^2 = $(CH_2)_2NHMe$) using sodium in boiling either "absolute butyl alcohol"[64] or "dehyd. ethanol".[48]

11. This product gave a picrolonate as light brown, tiny, crystalline aggregates from "alcohol", mp 220 °C (decomp)[63] while the picrolonate of (±)-noresermethole (**11**, R^1 = MeO, R^2 =R^3 = H, R^4 = Me) that was to be unequivocally synthesized by an application of Hoshino and Kobayashi's route (*vide supra*) has mp 221°C.[53] Similarly it afforded a deep red picrate as long rhombic plates from methanol, mp 159°C,[63] which would appear to be identical with the picrate (reddish-orange rhomboidal prisms from "alcohol", mp 162-163 °C[58] and dark red prisms from ethanol, mp 163-164 °C[97]) of (±)-noresermethole that was later respectively obtained by the Oxford group[58] (*vide supra*) and subsequently as an intermediate in a synthesis of (±)-eseramine *via* a Julian and Pikl type approach involving the reductive cyclization of **7** (R^1 = MeO, R^2 = CH_2CN) using sodium in dry ethanol boiling under reflux.[97]

12. Robert Robinson and his co-worker F. E. King sought to assign[68] these differences (NOTE 13) to variations in molecular geometry at the B/C ring junction of the 1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole system by their statement that "It is relevant to note that Linstead and Meade (J., 1934, 935) have isolated *cis*-*cis*- and *cis*-*trans*-isomerides of fused di*cyclo*octanes (two five-membered rings), and we provisionally regard the isomerism of *d*,*l*-eserethole-*a*, mp 38 °C (synthesised by Julian and Pikl, *loc. cit*), and our *d*,*l*-eserethole-*b*, mp 80 °C, as another case of the same kind. The fact that the behaviour of *d*,*l*-eserethole-*a* and *d*,*l*-eserethole-*b* towards methyl iodide is different is not surprising, because the stereochemical hypothesis closely concerns the configuration of the nitrogen atoms."[68] However, Robinson and King had failed to realize the effect on the eserethole tricyclic system of the aromatic ring A which, by forming a near-planar system with the ring B, thereby restricts the B/C ring junction to a *cis* fusion,[59] (see also refs 2, 11 and 98). No such restriction is present, of course, in Linstead and Meade's fused di*cyclo*octanes and the conclusion to be drawn, therefore, is that "all compounds containing the tricyclic ring system [as in eserethole] can exist in one configuration only, i.e. with the two pyrrole rings cis to each other, so that for each individual compound only one pair of

enantiomorphic forms is possible"[59] and that "All the experimental results so far obtained are in agreement with this hypothesis, and for each compound prepared only one pair of enantiomorphs has ever been obtained, never two pairs as would be predicted on the basis of the two asymmetric centres which the molecule contains."[59]

13. Earlier, along with M. Liguori,[58] they had also suggested that mp discrepancies might have resulted from either dimorphism ("It appears that the substance exists in two crystalline modifications"[58]) or even the "alternative hopeful idea of spontaneous resolution"[58] although this latter "did not survive the experimental test".[58]

ACKNOWLEDGMENTS

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