STUDIES IN THE ISOQUINOLINE SERIES

Part IV. Application of the Bruckner Method to the Synthesis of 3-, and 4-Arylisoquinolines

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BRUCKNER and co-workers[1] have developed an elegant method for the synthesis of 3-methylisoquinolines, in which the addition of dinitrogen trioxide to 1-arylpropenes constituted the first important step. The substitution of stilbenes and 1 : 1-diarylethylenes for 1-arylpropenes should lead to 3-, and 4-arylisoquinolines respectively and a study of the extension of the Bruckner method for this purpose is reported here.

Addition of dinitrogen trioxide to 3 : 4-methylenedioxystilbene proceeded with formation of the nitrosite in excellent yield. Acetylating decomposition of the nitrosite with acetic anhydride sulphuric acid mixture was slow and incomplete, but could be taken to near completion by recycling unchanged material with fresh acetic anhydride-sulphuric acid. Electrolytic reduction of the 1-acetoxy-1-(3 : 4-methylenedioxyphenyl)-2-nitro-2-phenylethane (I) so formed yielded N-acetyl-2-hydroxy-2-(3 : 4-methylenedioxyphenyl)-1-phenylethylamine (II) which was cyclised in good yield by phosphorus oxychloride in toluene to 6 : 7-methylenedioxy-1-methyl-3-phenylisoquinoline (III).

According to Shechter and Ley[2] the orientation in addition of dinitrogen trioxide to olefines is independent of the electronic demands of the groups attached to the unsaturated system. If this were so, two nitrosites should have been formed from 3 : 4-methylene dioxystilbene, but neither at the stage of addition of dinitrogen trioxide, nor at any of the subsequent stages in the sequence outlined above, could we detect more than one compound. A single nitrosite appeared to be formed, the one in which the nitro group was attached to the carbon atom β- to the 3 : 4-methylenedioxyphenyl group.

Addition of dinitrogen trioxide to 1 : 1-diphenylethylene proceeded smoothly with formation of a crystalline nitrosite in excellent yield. Treatment of the nitrosite with acetic anhydride-sulphuric acid yielded 1 : 1-diphenyl 2-nitroethylene. Similarly, nitrosites from 1 : 1-di-*p*-tolylethylene, 1 : 1 : 2-

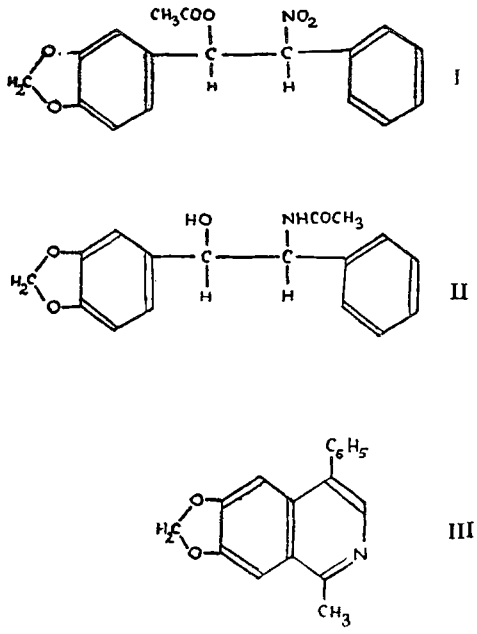


FIG. 1.

triphenylethylene and 1 : 1-diphenylpropylene, which could not be obtained in crystalline condition, reacted with acetic anhydride-sulphuric acid with evolution of nitrous fumes and formation of the corresponding nitroolefines. Treatment of 1 : 1-di-*p*-anisylethylene with dinitrogen trioxide led to the nitroolefine as the only isolable product. The decomposition of the nitrosites to nitroolefines proceeds apparently through the formation of an intermediate carbonium ion since electron-releasing groups in the aryl nuclei facilitate the reaction. The nitrosites from 1 : 1-diarylethylenes are thus seen

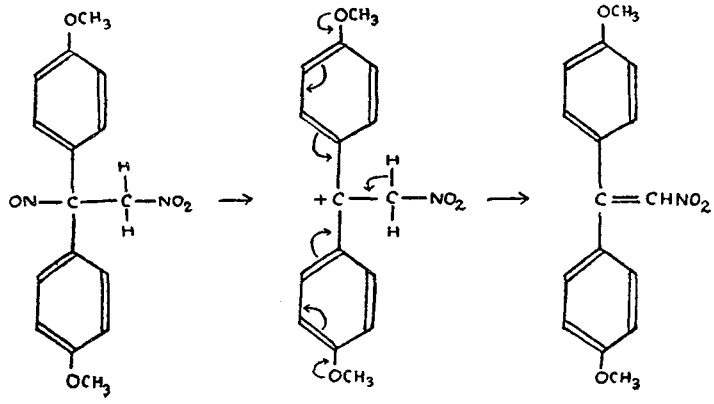
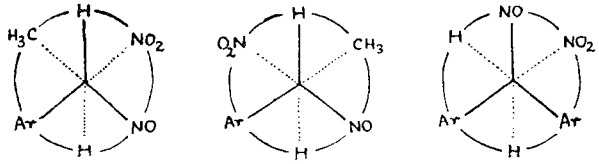


FIG. 2.

to decompose into nitroolefines by treatment with acetic anhydride-sulphuric acid mixture whereas nitrosites from 1-arylpropenes[1, 3] are changed to acetoxynitro compounds. A plausible explanation for this difference may be furnished. Addition of dinitrogen trioxide to an 1-arylpropene may conceivably lead to two diasteroisomers, although a single product is obtained, addition being apparently stereospecific. The most stable conformations of the two possible diasteroisomers may be shown as in Fig. 3 A and B. In either case, the nitroso group is not coplanar with the hydrogen



A B C

FIG. 3

atom on the β-carbon atom and this can be brought about only in more unfavourable conformations than those represented for the diasteroisomers. Reactions with acetic anhydride-sulphuric acid mixture proceeds with substitution rather than elimination.

In the case of nitrosites from 1 : 1-diarylethylenes the most stable conformation may be represented as in Fig. 3 C, an arrangement in which the nitroso group and the hydrogen atom on the β-carbon atom are coplanar, a condition favouring elimination, rather than substitution.

1 : 1-Diphenyl-2-nitroethylene was reduced to 2 : 2-diphenylethylamine by lithium aluminium hydride in excellent yield. The N-acetyl derivative of the amine was cyclised by heating with phosphorus pentoxide in xylene to 3 : 4-dihydro-1-methyl-4-phenylisoquinoline which was then dehydrogenated by heating with palladium black in refluxing decalin solution to 1-methyl-4-phenylisoquinoline.

1 : 1-Di-*p*-tolyl-2-nitroethylene, 1 : 1-di-*p*-anisyl-2- nitroethylene, 1 : 1-diphenyl-2-nitro-Δ′-propylene were carried through a similar sequence of reactions for obtaining 1 : 7-dimethyl-4-*p*-tolyl-, 1-phenyl-2-methyl-4-*p*-tolyl-, 4-*p*-anisyl-7-methoxy-1-methyl-, 4-*p*-anisyl-7-methoxy-1-phenyl-, 3-methyl-1 : 4-diphenyl-, and 1 : 3-dimethyl-4-phenyl-3 : 4-dihydroisoquinolines. Cyclisation of N-acetyl-1 : 2 : 2-triphenylethylamine and N-benzoyl-1 : 2 : 2-triphenyl-ethylamine to the corresponding 3 : 4-dihydroisoquinolines could not be effected.

EXPERIMENTAL

I. 6 : 7-*Methylenedioxy*-1-*methyl*-3-*phenylisoquinoline*

(*a*) 3 : 4-*Methylenedioxystilbene nitrosite*.—A solution of 3 : 4-methylenedioxystilbene (1 g.) in ether (50 ml.) was kept over a saturated solution of sodium nitrite (50 ml.) and treated dropwise with sulphuric acid (4 N). During the course of a few hours a pale yellow crystalline solid separated. This was filtered, washed with water and dried in a desiccator. It decomposed at 136–38° (Found: N, 8·9. $C_{15}H_{12}O_5N_2$ requires N, 9·3%).

(*b*) 1-*Acetoxy*-1- (3 : 4-*methylenedioxyphenyl*)-2-*nitro*-2-*phenylethane*.—A suspension of the above nitrosite (20 g.) in acetic anhydride (60 ml.) was treated under vigorous stirring with acetic anhydride (6 ml.) containing sulphuric acid (2 ml.). After stirring for 6 hr., the solution was filtered (residue A). The filtrate was treated with crushed ice and the sticky solid that separated was washed with water and triturated with methanol. The solid obtained was recrystallised from alcohol, yielding crystals, m.p. 146–47° (Found: C, 62·3; H, 4·7; N, 4·3. $C_{17}H_{15}O_6N$ requires C, 62·0; H, 4·6; N, 4·3%). Residue (A) which was unreacted nitrosite was again treated with acetic anhydride-sulphuric acid as before. In all 14 g. of the nitrocompound were obtained.

(*c*) *N-Acetyl*-2-*hydroxy*-2-(3 : 4-*methylenedioxyphenyl*)-1-*phenylethylamine*.—The foregoing nitro compound (5 g.) was reduced electrolytically as described earlier.[3] The *acetylamino* compound (3 g.) was crystallised from toluene yielding crystals, m.p. 169° (Found: C, 68·8; H, 5·5; N, 4·5. $C_{17}H_{17}O_4N$ requires C, 68·2; H, 5·7; N, 4·6%).

(*d*) 6: 7-*Methylenedioxy*-1-*methyl*-3-*phenylisoquinoline*.—The foregoing amide (1 g.) was refluxed in dry toluene (10 ml.) with phosphorus oxychloride (3 ml.) for 1 hr. The product was isolated in the usual way. The *isoquinoline* was obtained as colourless needles from alcohol, m.p. 138° (Found: C, 77·1; H, 4·4; N, 5·4. $C_{17}H_{13}O_2N$ requires C, 77·6; H, 5·0; N, 5·3%).

The hydrochloride was obtained as a bright yellow solid sparingly soluble in water and was recrystallised from alcohol, m.p. 260°.

II. 1-*Methyl*-4-*phenylisoquinoline*

(*a*) 1 : 1-*Diphenylethylene nitrosite*.—A solution of 1 : 1-diphenylethylene (1 g.) in ether (20 ml.) was treated with a saturated solution of sodium nitrite (20 ml.). Dilute sulphuric acid was added dropwise. The ether layer turned blue and the reaction was complete when the blue colour changed to yellow. The ether was allowed to evaporate spontaneously and the sticky residue

washed thoroughly with water and dried in a desiccator. Recrystallisation from ether-petroleum ether mixture gave white feathery crystals (1 g.), decomposing at 106° (Found: N, 11·1. $C_{14}H_{12}N_2O_3$ requires N, 10·9%).

(*b*) 1: 1-*Diphenyl-2-nitroethylene.*—The above nitrosite (14 g.) was refluxed with acetic anhydride (42 ml.) containing a drop of concentrated sulphuric acid when the evolution of nitrous fumes had ceased, the solution was cooled and poured into water (200 ml.) to decompose the acetic anhydride. The aqueous layer was decanted from the heavy oil, which was further washed with water. On stirring with alcohol, a yellow crystalline solid separated which on recrystallisation from alcohol melted at 92°, yield 9 g. (Found: C, 74·6; H, 5·1; N, 6·4. $C_{14}H_{11}O_2N$ requires C, 74. 7; H, 4·9; N, 6·2%).

(*c*) 2: 2-*Diphenylethylamine.*—A solution of the foregoing nitro compound (8 g.) in absolute ether (300 ml.) was added to a stirred suspension of lithium aluminium hydride (5 g.) in absolute ether (100 ml.), the reaction vessel being provided with an efficient condenser and protected from moisture. The solution was stirred for a further 2 hr., after completion of addition, left overnight and decomposed cautiously with water. The ether layer was decanted off and the residue thoroughly extracted with ether. Removal of the ether yielded an oil (6 g.) purified by distillation *in vacuo*, b.p. 175°/20 mm. n_D^{30}, 1·569. The acetyl derivative prepared in the usual way was recrystallised from petroleum ether (b.p. 40–60°) yielding colourless crystals, m.p. 91° (Found: N, 6·1. $C_{16}H_{17}ON$ requires N, 5·9%).

(*d*) 1-*Methyl-4-phenylisoquinoline.*—The above acetyl derivative (2 g.) was dissolved in dry xylene (25 ml.) and heated on a sand-bath under gentle reflux for 4 hr., after adding phosphorus pentoxide (5 g.). After cooling, the excess phosphorus pentoxide was decomposed by the cautious addition of crushed ice. The xylene layer was separated and the aqueous layer made strongly alkaline with sodium hydroxide solution. The liberated base was extracted with ether. Removal of the ether yielded 3: 4-*dihydroisoquinoline* (0·4 g.) characterised as the picrate, m.p. 170° (*cf.* Dey and Ramanathan[4]).

0·4 g. of the dihydroisoquinoline was dehydrogenated by refluxing in decalin (50 ml.) with palladium black (50 mg.) in a current of carbon dioxide, till the evolution of hydrogen ceased. The catalyst was filtered off, the decalin solution extracted thrice with dilute hydrochloric acid (4 N) and the combined acid extract basified with sodium hydroxide solution. The liberated base was isolated by ether extraction and characterised as the *picrate*, m.p. 226° (Found: C, 59·0; H, 4·0. $C_{22}H_{16}O_7N_4$ requires C, 58·9; H, 3·6%). The base regenerated from the picrate and purified by sublimation *in vacuo* melted at 80°.

III. 3:4-*Dihydro*-1:7-*dimethyl*-4-p-*tolyl- and* 3:4-*dihydro*-7-*methyl*-1-*phenyl*-4-p-*tolylisoquinoline*

(*a*) 1:1-*Di*-p-*tolyl*-2-*nitroethylene*.—1:1-Di-*p*-tolylethylene was converted to the nitrosite as previously in 1 g. batches. The nitrosite was obtained as a thick yellow oil which failed to crystallise. The crude nitrosite (7 g.) was treated with acetic anhydride (10 ml.) containing sulphuric acid (2 drops). The solution warmed up considerably with evolution of nitrous fumes. After cooling, the excess acetic anhydride was decomposed by water and the heavy oil which separated solidified. Recrystallisation from ethyl alcohol yielded crystals of the nitro compound (4 g.), m.p. 115° (Found: C, 75·5; H, 5·7; N, 5·8. $C_{16}H_{15}NO_2$ requires C, 75·9; H, 5·9; N, 5·5%).

(*b*) 2:2-*Di*-p-*tolylethylamine*.—The foregoing nitro compound (4 g.) reduced with lithium aluminium hydride yielded the amine (3 g.) as a pale yellow oil, b.p. 185–90°/7 mm. The *hydrochloride* prepared as usual and recrystallised from alcohol-ether melted at 235° (Found: C, 72·9; H, 7·2; N, 5·8. $C_{16}H_{20}NCl$ requires C, 73·3; H, 7·7; N, 5·4%). The *acetyl* derivative was obtained as an oil. The *benzoyl* derivative crystallised from alcohol as needles, m.p. 136° (Found: C, 84·1; H, 7·5; N, 4·6. $C_{23}H_{23}ON$ requires C, 83·9; H, 6·9; N, 4·3%).

(*c*) 3:4-*Dihydro*-1:7-*dimethyl*-4-p-*tolylisoquinoline*.—The oily acetyl derivative (0·6 g.) above was cyclised by refluxing in dry toluene (10 ml.) with phosphorus oxychloride (3 ml.) for 4 hr. The base was isolated in the usual way and characterised as a picrate recrystallised from alcohol, m.p. 187° (Found: C, 59·9; H, 4·8; N, 11·5. $C_{24}H_{22}O_7N_4$ requires C, 60·3; H, 4·6; N, 11·7%).

(*d*) 3:4-*Dihydro*-7-*methyl*-1-*phenyl*-4-p-*tolylisoquinoline*.—The benzoyl derivative (0·5 g.) above on cyclisation under similar conditions yielded the dihydroisoquinoline (0·03 g.) as an oil, characterised as the picrolonate, m.p. 176° (Found: C, 68·7; H, 5·6; N, 11·6. $C_{33}H_{29}O_5N_5$ requires C, 68·9; H, 5·0; N, 12·2%).

IV. 4-p-*Anisyl*-3:4-*dihydro*-7-*methoxy*-1-*methyl and* 1-*phenylisoquinolines*

(*a*) 1:1-*Di*-p-*anisyl*-2-*nitroethylene*.—1:1-di-*p*-anisylethylene (2 g.) was treated with dinitrogen trioxide as previously yielding a yellow solid admixed with a red liquid. The solid was removed mechanically and recrystallised from alcohol yielding crystals (1·0 g.), m.p. 116° (Found: C, 67·1; H, 5·3; N, 4·9. $C_{16}H_{15}O_4N$ requires C, 67·4; H, 5·3; N, 4·9%). The red liquid solidified gradually and was recrystallised from alcohol yielding crystals (0·05 g.), m.p. 123° (Found: C, 67·9; H, 5·7; N, 4·4. $C_{16}H_{15}O_4N$ requires

C, 67·4; H, 5·3; N, 4·9%). This is probably a dimorphic form of the nitro compound, m.p. 116°.

(*b*) 2: 2-*Di*-p-*anisylethylamine.*—Reduction of the nitro compound, m.p. 116° above (7 g.) with lithium aluminium hydride yielded the amine (3 g.) as a thick brown oil, b.p. 210–12°/7 mm. The *acetyl* derivative melted at 123° (Found: C, 72·7; H, 6·6; N, 4·6. $C_{18}H_{21}O_3N$ requires C, 72·2; H, 7·0; N, 4·7%). The *benzoyl* derivative melted at 153° (Found: C, 76·5; H, 6·2; N, 4·1. $C_{23}H_{23}O_3N$ requires C, 76·5; H, 6·4; N, 3·9%).

(*c*) 4-p-*Anisyl*-3: 4-*dihydro*-7-*methoxy*-1-*methylisoquinoline.*—The acetyl derivative above (0·5 g.) was cyclised as usual and the base (0·02 g.) obtained as an oil characterised as the picrolonate, which did not melt up to 360° (Found: N, 12·7. $C_{28}H_{27}N_5O_7$ requires N, 12·8%).

(*d*) 4-p-*Anisyl*-3: 4-*dihydro*-7-*methoxy*-1-*phenylisoquinoline.*—The above benzoyl derivative was cyclised by phosphorus oxychloride in toluene, to yield the *base* crystallised from alcohol as colourless plates, m.p. 226° (Found: N, 4·3. $C_{23}H_{21}O_2N$ requires N, 4·1%).

V. 3: 4-*Dihydro*-1: 3-*dimethyl*-4-*phenyl- and* 3: 4-*dihydro*-3-*methyl*-1: 4-*diphenylisoquinolines*

(*a*) 2: 2-*Diphenylisopropylamine.*—1:1-Diphenylpropylene was treated with dinitrogen trioxide as earlier. The nitrosite obtained as an yellow oil was treated with acetic anhydride containing two drops of sulphuric acid. The nitroolefine isolated as usual was a heavy yellow oil which could not be induced to solidify. It was reduced by lithium aluminium hydride to 2: 2-diphenylisopropylamine obtained as colourless needles, m.p. 52°, from petroleum ether (b.p. 40–60°) (Found: C, 84·8; H, 8·3. $C_{15}H_{17}N$ requires C, 85·3; H, 8·1%).

The *acetyl* derivative recrystallised from petroleum ether (b.p. 40–60°) as needles, m.p. 111° (Found: C, 80·2; H, 7·2; N, 5·4. $C_{17}H_{19}ON$ requires C, 80·6; H, 7·5; N, 5·5%).

The *benzoyl* derivative recrystallised from alcohol melted at 199° (Found: C, 84·1; H, 6·4; N, 4·4. $C_{22}H_{21}ON$ requires C, 83·8; H, 6·7; N, 4·4%).

(*b*) 3: 4-*Dihydro*-1: 3-*dimethyl*-4-*phenylisoquinoline.*—The acetyl derivative above was cyclised as usual yielding the base characterised as the picrolonate, m.p. 224° (Found: N, 14·3. $C_{27}H_{25}O_5N_5$ requires N, 14·0%).

(*c*) 3: 4-*Dihydro*-3-*methyl*-1: 4-*diphenylisoquinoline.*—The benzoyl derivative above on cyclisation yielded the base as an oil, characterised as the

hydrochloride, m.p. 210° (Found: C, 79·6; H, 5·7. $C_{22}H_{20}NCl$ requires C, 79·2 ; H, 6·0%).

VI. 1 : 2 : 2-*Triphenylethylamine*

(*a*) 2-*Nitro*-1 : 1 : 2-*triphenylethylene*.—1 : 1 : 2-Triphenylethylene was treated with dinitrogen trioxide as usual. The nitrosite obtained as an oil on treatment with acetic anhydride-sulphuric acid yielded the nitro compound, m.p. 178° (Found: C, 80·2; H, 4·8; N, 4·7. $C_{20}H_{15}O_2N$ requires C, 79·7; H, 5·0; N, 4·7%).

(*b*) 1 : 2 : 2-*Triphenylethylamine*.—Reduction of the foregoing nitro compound with lithium aluminium hydride yielded the amine, b.p. 210–12°/7 mm. The *acetyl* derivative recrystallised from alcohol melted at 208° (Found: C, 83·4; H, 6·7; N, 4·4. $C_{22}H_{21}ON$ requires C, 83·8; H, 6·7; N, 4·4%).

The *benzoyl* derivative recrystallised from alcohol melted at 230° (Found: C, 85·9; H, 6·2; N, 3·9. $C_{27}H_{23}ON$ requires C, 85·9; H, 6·1; N, 3·7%).

SUMMARY

The Bruckner method has been extended to the study of 3-, and 4-arylisoquinolines.

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