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Synthesis of 9, 10- Dihydrolysergic Acid

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Abstract: 9, 10- Dihydrolysergic acid has been obtained from lysergol with overall 40% yield. The catalytic reduction of $\Delta^{9,10}$ double bond in lysergol, protection of hydroxyl group as t-BDMSilyl ether and NH as N-BOC derivative followed by treatment with TBAF gave 1-(t butoxy carbonyl)- 9,10-dihydrolysergol. The oxidation using TEMPO and IDBA in dichloromethane followed by deprotection of N- BOC resulted in 9, 10-dihydrolysergic acid.
Key words: TBAF, TEMPO / IBDA oxidation, Dihydrolysergol, N- BOC.

I. INTRODUCTION

The potent and versatile physiological activities of natural ergot alkaloids prompted a thorough chemical and pharmacological investigation of this class of natural product for many years[1-7]. From numerous structural modifications[8], the ergolenes and ergolines have emerged important drugs of high potency in the treatment of various disorders, such as, e.g. uterine atonia, orthostatic circulatory disturbance, senile cerebral insufficiency, hypertension, acromegaly and parkinsonism [9-17]Many the rapeutically used ergot alkaloids belong to the peptide alkaloids but a significant number is synthetically prepared whose production is based on few precursors e.g. lysergic acid, 9, 10- dihydrolysergic acid, 9, 10- dihydrolysergol etc. [18].9, 10- dihydrolysergic acid is precursor of many pharmaceutically active ergot alkaloids. N- acylurea derived from 9, 10- dihydrolysergic acid is called cabergoline which is a potent prolactin inhibitor. It is marketed by Pharmacia as 'Dostinex' for the treatment of many CNS disorders and is also being investigated for the management of Parkinson's disease [19]. The 9, 10- dihydro derivatives of the ergotamine and ergotoxine are therapeutics for cardiovascular diseases [20].

Owing to the importance of 9, 10- dihydrolysergic acid as a precursor for various biological active ergot alkaloids, the present synthetic studies have been carried out. In literature some methods for the synthesis of 9, 10- dihydrolysergic acid have been reported. An obvious approach to 9, 10- dihydrolysergic acid is to start with lysergic acid or its isomer paspalic acid [9],both of which are accessible via microbial fermentation on a technical scale [9, 21]. Another starting material for the synthesis is 9, 10- dihydrolysergic acid methyl ester. Lysergol was hydrogenated to 9, 10- dihydrolysergol. The primary hydroxyl group was hydrogenated as t-BDMSilyl ether followed by N-1 acetylation with acetyl chloride. The 1N-acetyl 9, 10- dihydro t-BDMSilyl ether was deprotected with BF_3. Et_2O to give 1N-acetyl 9, 10- dihydrolysergol in overall 43% yield. The oxidation of 1N-acetyl 9, 10- dihydrolysergol with Swern oxidation (DMSO/ TFAA) yielded 1N-acetyl 9, 10- dihydrolysergal in 62% yield. But, during this oxidation reaction 1N-acetyl 9, 10- dihydrolysergal isomerised to 1N-acetyl iso- 9, 10- dihydrolysergal. After the hydrolysis of 1N-acetyl 9, 10- dihydrolysergal using potassium carbonate in methanol afforded a mixture a of 9,10- dihydrolysergal accompanied by its hemiacetal and by traces of presumed 8- epi analogues. The oxidation of 9,10- dihydrolysergal using m-CPBA followed by subsequent esterification gave 9,10- dihydromethyl lyergate in 80% yield. Finally 9,10- dihydromethyl lyergate can be hydrolyse to 9,10- dihydromethyl lysergic acid [9, 21]. But, this approach for the synthesis of 9,10- dihydromethyl lysergic acid cannot be used. A major drawback of this approach is the formation of side products and epimerisation in the final stages of the synthesis. Thereby, the overall yield of the desired product decreased significantly.

Another method reported in the literature includes protection of hydroxyl group as t-BDMSilyl ether first followed by N-1 and N-6 BOC protection with BOC anhydride. The hydroxyl group of 9,10- dihydrolysergol was protected as t-BDMSilyl ether in 88% yield. The N-1 and N-6 were protected with BOC anhydride and hydroxy group was deprotected to give 1,6- di(t-butoxycarbonyl) 9,10 dihydrolysergol in 80% yield. The hydroxy group was oxidised to carboxylic acid in 88.5% yield. The N-1 and N-6 deprotection and esterification was carried out using methanol and thionyl chloride. The ester was isolated as hydrochloride salt in 94.5% yield.

But, the main drawback of this synthesis is the same as earlier synthesis. Here in this synthesis N-1 and N-6 are protected simultaneously. Thus, the overall yield of the final product is affected.

In the present paper the synthesis of 9,10- dihydrolysergic acid from lysergol is reported. The primary hydroxyl group was protected as silyl ether and N-1 was protected with BOC anhydride. 1N-BOC protected 9,10- dihydrolysergol was oxidised using TEMPO oxidation. The deprotection of 1N-BOC with TBAF gave 9, 10- dihydrolysergic acid and no side product was formed.

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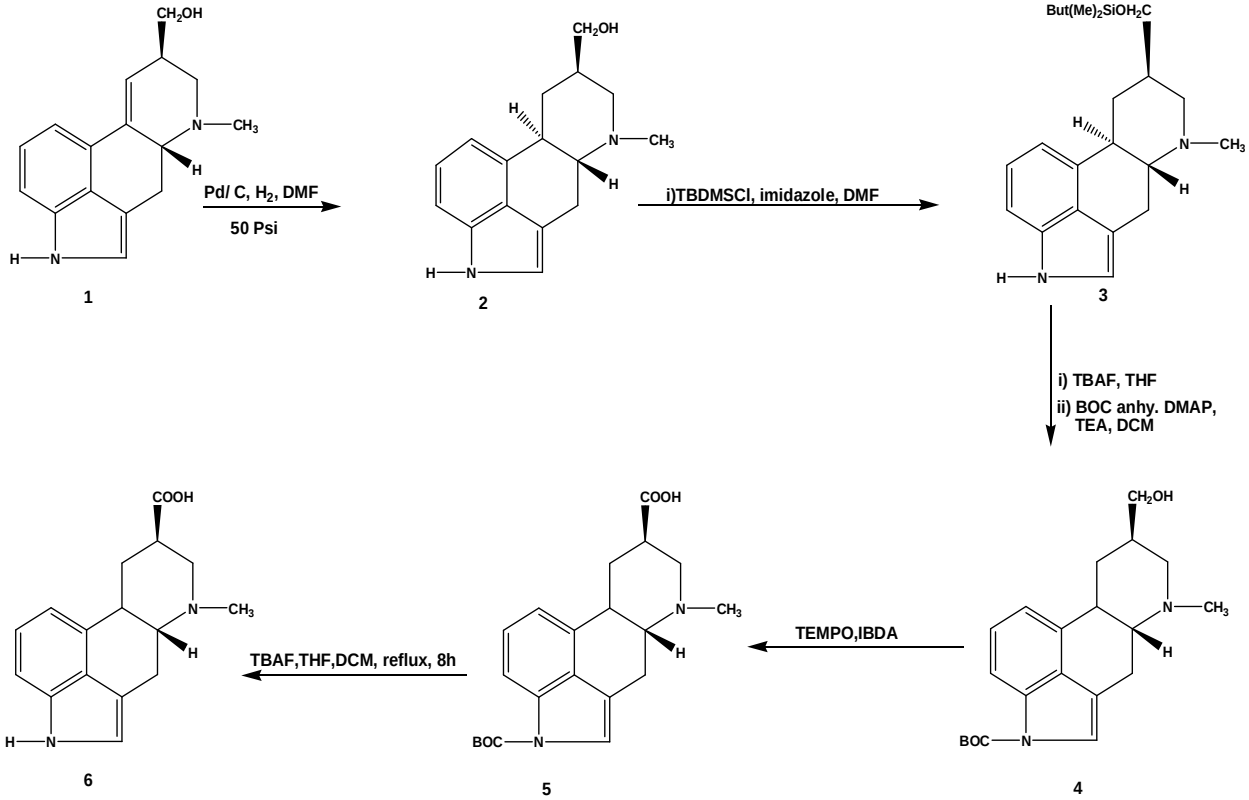
II. RESULTS AND DISCUSSION

The synthesis of 9,10- dihydrolysergic acid (6), a key intermediate for a number of pharmacological active compounds has been carried out from a commercially available starting material lysergol (1). For obtaining9,10- dihydrolysergic acid from lysergol two main strategies have been investigated. First, oxidation of primary hydroxyl group to acid and the reduction of $\Delta^{9,10}$ of double bond. Second, reduction of $\Delta^{9,10}$ of lysergol followed by oxidation to 9,10- dihydrolysergic acid. In fact, the versatile methodologies for oxidation that found general application in preparative organic chemistry failed in the oxidation of lysergol directly to lysergic acid [9].Since lysergol is poorly soluble in less polar organic solvents and reactions such as oxidation are generally carried out in non polar solvents. Thus the poor solubility of lysergol [5] in these solvents has a major role in the failure of oxidation of lysergol to lysergic acid. This prompted us to adopt the second strategy which involves hydrogenation of lysergol to 9, 10- dihydrolysergol followed by oxidation to 9,10- dihydrolysergic acid. Since, 9,10- dihydrolysergol is soluble in nonpolar solvents so the solubility problem to carry out oxidation has been solved. Before oxidation reaction the functional group N-H was to be protected. For the protection of N-H group we needed to protect OH group. Otherwise O-H would have interfered during N-H group protection. So firstly lysergol (1)was reduced to 9,10- dihydrolysergol (2) using Pd/ C catalyst in DMF in 86.59% yield. Before the protection of N-H group the protection of hydroxyl group as t- Butyldimethyl silyl ether was carried out using TBDMSCl in 85.83% yield. The silyl etherwas reacted with BOC anhydride and dimethyl aminopyridine for protection N-H group to give 8- (tert- Butyl dimethylsilyloxymethyl) 9, 10- dihydrolysergol (3 in 86.07 % yield. Simultaneously, deprotection of hydroxyl group was carried out using tetra-butylammonium fluoride (TBAF) to give 1-N BOC protected 9, 10- dihydrolysergol (4) in 97.44 % yield. The oxidation of this alcohol using 2,2,6,6-Tetramethylpiperidinyloxy (TEMPO) and iodosobenzene diacetate (IBDA) gave a hygroscopic yellow solid, 1N-BOC 9,10- dihydrolysergic acid (5)in 85% yield. Since this compound was hygroscopic it was to be kept nitrogen atmosphere and its reaction were to be carried out in anhydrous conditions carefully. Finally, the 1-N BOC group was to be deprotected TBAF in THF to give 9,10- dihydrolysergic acid (6) in 64% yield.



Scheme: Synthesis of 9, 10- dihydrolysergic acid from lysergol.

III. CONCLUSION

The synthesis of 9, 10- dihydrolysergic acid from lysergol, a commercially available starting material has been achieved. As compared to the previously reported procedures, the present process does not yield to a mixture of products. Thus the overall yield is

better. The protection of hydroxyl group and N-1 followed by deprotection of hydroxyl group and its oxidation resulted in the final product 9, 10- dihydrolysergic acid. The overall yield of the reaction is 40%.

IV. EXPERIMENTAL

Equipments/ chemicals Infrared spectra (IR) were recorded using Perkin Elmer Model 1430 spectrophotometer with potassium bromide (KBr) palette. Only principal absorption bands of interest are reported and expressed in cm^{-1}. The ^{1}H NMR and ^{13}C NMR spectra were recorded

in DMSO-$d_6$and $CDCl_3$on Varian 400 spectrometer operating at 400 MHz and 100 MHz, respectively, with TMS as an internal standard. Chemical shifts are given in ppm relative to tetramethyl silane as an internal standard (δ= 0 ppm) for ^{1}H NMR and DMSO-d_6 (δ= 39.50ppm) for ^{13}C NMR spectra. For ^{1}H NMR and ^{13}C NMR spectra, chemical shifts are in parts per million relative to TMS. TLC analysis was performed in Chloroform: Methanol (8:2) and examined under UV light 400nm- 315 nm (UV A), 315 nm- 280 nm (UV B). Flash chromatography was performed by using 40- 63 µm silica gel (230- 400 mesh) and applying nitrogen pressure from the top of the column.

9, 10-Dihydrolysergol (2): To a solution of lysergol (5.50 g, 21.65 mmol) in DMF (55 mL) was added palladium on carbon (5%, 170 mg). The hydrogenation was carried out at $60^{0}C$ using hydrogen gas pressure 50 psi for 2h. After 2h the reaction mixture was cooled, filtered to remove the catalyst and the residue was washed with DMF (2x5 mL). The filtrate was evaporated to dryness and suspended in water (50 mL). The resulting suspension was filtered, washed with water (3x10 mL) and dried to give grey solid (4.8 g, 95.43%), m.p. 275°C (Lit. [23] m.p. 280°C). IR (KBr, cm^{-1}):3405.1, 3060.5, 2940.8, 2886.9, 2822.1, 2362.8, 1884.6, 1818.1, 1609.5, 1461.1, 1441.1, 1372.7, 1345.0, 1328.9, 1293.3, 1220.7, 1195.3, 1125.9, 1068.0, 1029.8, 980.9, 944.9, 917.6, 892.3, 840.1, 798.2, 781.4, 750.3, 627.4, 565.8, 529.5, 490.5, 459.0^{1}H NMR ($CDCl_3$, 400MHz, δppm): 1.06- 1.15 (q, 1H, H- 9a), 1.96- 2.01 (t, 1H, H-7a), 2.11-2.13 (m, 2H, H-5, H-8), 2.49 (s, 3H, N-CH_3), 2.56-2.59 (m, 2H, H-9e, H-4a), 2.90- 2.96 (t, 1H, H-10), 3.38-3.43 (dd, 1H, H-4e), 3.46- 3.50 (m, 1H, H-17u), 3.50- 3.56(m, 1H, H-17d), 4.28 (s, 1H, CH_2OH), 6.85 (m, 2H, H-2, H-14), 7.05-7.07 (m, 1H, H-13), 7.09-7.17 (m, 1H, H-12), 7.67- 7.67- 7.68 (m, 1H, N-H). ^{13}CNMR ($CDCl_3$, 100 MHz, δppm): 26.87 (C4), 30.93 (C9), 38 45(C-8), 40.31(C10), 43.21 (N-CH_3), 60.87(C7), 65.22 (C-17), 67.50 (C5), 108.90 (C14), 110.42 (C3), 11.48 (C12), 118.38 (C2), 122.4 (C13), 128.20 (C16), 132.84 (C11), 133.47 (C15). Positive ESIMS (m/z) 257.2

8- (tert- Butyl dimethylsilyloxymethyl) 9, 10- dihydrolysergol (3): 9-10-Dihydrolysergol (5.0 g, 19.53 mmol), TBDMSCl (3.8 g, 27.5mmol) and imidazole (3.12 g, 45.80 mmol) were dissolved in dry DMF (46 mL). The reaction mixture was stirred under nitrogen atmosphere at room temperature for 5 h. The contents were poured into saturated $NaHCO_3$ (390 mL) and grey precipitates were filtered, washed with water (50 mL) and dried to give grey powdered solid (6.18 g, 86.07%), melting point 269° C. IR (KBr, cm^{-1}) 3851, 3749, 3147, 3054, 2946, 2857, 2795, 2367, 1727, 1653, 1611, 1464, 1391, 1356, 1252, 1094, 1035, 927, 841, 777, 742, 669, 624, 486.^{1}H NMR ($CDCl_3$, 400 MHz, δppm): 0.0054- 0.015 (s, 6H, $SiCH_3$), 0.79-0.84 (s, 9H, CMe_3), 1.02- 1.11 (1H, q, H9a), 1.85- 1.91 (1H, m, H7a), 2.03- 2.09 (m, 2H, H5, H8), 2.40 (s, 3H, N-CH_3), 2.54- 2.65(m, 2H, H4a, H9e), 2.87- 2.9 (dt, 1H, H10), 3.03- 3.07 (dd, 1H, H7e), 3.31- 3.35 (dd, 1H, H4e), 3.42- 3.46 (dd,1H, H- 17a), 3.53-3.56 (dd, 1H, H-17d), 6.75 (s, 1H, H-2), 6.83- 6.86(m, 1H, H-12), 7.05-7.15(m, 2H, H-13, H- 14) 8.04 (s, 1H, N-H). ^{13}CNMR ($CDCl_3$, 100 MHz, δppm): -5.31 ($SiCH_3$), 18.39 (SiC), 26.00 (CMe_3), 27.05 (C4), 30.74 (C9), 38.66 (C8), 40.50 (C10), 43.46 (NCH_3), 60.97 (C7), 66.58 (C17), 67.41 (C5), 108.50 (C14), 112.05 (C3), 113.16 (C12), 117.75 (C2), 123.07 (C13), 126.26 (C16), 133.35 (C11), 133.65 (C15).

1-(t-butoxycarbonyl) – 9, 10- dihydrolysergol (4) : 17-O- (t- Butyl dimethylsilyl) 9, 10- dihydrolysergol (6.3 gm, 17.119 mmol) was dissolved in DCM (30mL). Triethyl amine (3.56 g, 35.24 mmol), dimethylaminopyridine (0.432 g, 2.09 mmol), ditertiary butyl-dicarbonate (4.63 g, 21.23 mmol) was added and the mixture was stirred for 5 h at room temperature. It was diluted with water (100 mL). Organic layer was washed with water (30 mL), brine (30 mL) and dried over sodium sulphate. After evaporation a brown residue was obtained. It was dissolved in dry THF (42 mL) and solution of tetrabutylammoniumfluoride (5.026 g, 25.8 mmol) in THF (10 mL) was added. The reaction mixture was stirred at room temperature for 5 h and was concentrated under vacuum to about 10 mL. The residue was stirred with water (20 mL). The residue was dissolved in approximately DCM (30 mL). The DCM layer was washed with CH_3COOH (10%, 10 mL), then with water. The DCM layer was washed with brine (5 mL) dried over sodium sulphate and evaporated to give the brown residue (5.72 g, 97.44%), 220 °C (charring). IR(KBr, cm^{-1}): 3329, 2979, 2930, 2681, 2580, 2490, 1727, 1559, 1483, 1442, 1396, 1363, 1283, 1252, 1171, 1152, 1128, 1101, 1077, 1016, 972, 946, 857, 758, 651, 608, 523. ^{1}H NMR ($CDCl_3$, 400 MHz, δppm): 0.99- 1.02 (t, 1H, H9a), 1.37 (m, 1H, H7a), 1.66 (s, 9H, Cme_3), 2.00-2.05 (m, 1H, H8), 2.69 (s, 3H, NCH_3), 2.82-2.88 (m, 3H, H4a, H9e, H10), 3.20-3.31 (m, 2H, H5, H4e), 7.04 (d, 1H, H-12), 7.26-7.32 (m, 2H, H13), 7.79 (s, 1H, H14). ^{13}C NMR ($CDCl_3$, 100 MHz, δppm):13.7 (CMe), 19.77 (C17), 25.65 (C4), 29.43 (C9), 37.86 (C10), 59.61 (C7), 66.98 (C5), 83.78 (C-O), 113.50 (C3), 113.68 (C13), 117.21 (C12), 119.94 (C2), 125.58 (C16), 130.56 (C8).

1-N-(t-butoxycarbonyl)-9, 10- dihydrolysergic acid (5): To a solution of 1-(t-butoxycarbonyl) – 9, 10- dihydrolysergol (1.16g, 3.25mol) in dichloromethane (20 mL) and water (0.5 mL) was added, TEMPO (0.22 g). The solution was cooled in ice bath and iodobenzene diacetate (5.92 mol) was added in portions. The mixture was stirred at room temperature for 16 hours. The reaction was quenched with the addition of sodium thiosulphate solution (1.82 g in 15 mL water) and organic layer was separated. The aqueous layer was extracted with DCM (10 mL) and the combined DCM layers were washed with water (20 mL), brine (10 mL), dried over sodium sulphate and evaporated to give brown viscous residue. The residue was crystallized in cold methanol to yield 1-N-(tert-butoxy-carbonyl)-ergoline-8β-carboxylic acid as yellow solid (hygroscopic) (2.42 g, 85%). IR (KBr, cm^{-1}): 3318, 2971, 2919, 2676, 2580, 2539, 2489, 2365, 1730, 1715, 1655, 1582, 1439, 1395, 1364, 1345, 1303, 1238, 1249, 1166, 1149, 1131, 1102, 1078, 1056, 1019, 979, 947, 878, 856, 825, 753, 731, 655, 603, 492, 470. ^{1}H NMR($CDCl_3$, 400 MHz, δppm): 1.14- 1.29 (m, 2H, H9a, H- 7a), 1.66-1.69 (s, 9H, Cme_3), 2.02 (s, 1H, H8), 2.13-2.15 (m, 1H, H5), 2.55 (s, 3H, N-CH_3), 2.65-2.68 (d, 1H, H4a), 2.99-2.97 (dt, 1H, H10)3.22-3.23 (d, 1H, H4e), 3.28-3.32 (dd,1H, H7e), 7.06-7.08 (2, 1H, H12), 7.14-7.73(m, 2H, H13, H2), 7.73-7.75 (m, 1H, H14). ^{13}C NMR ($CDCl_3$, 100 MHz, δppm): 21.58 (C17), 25.60 (C4), 28.21 (CMe_3), 30.40 (C9), 38.15 (C8), 39.76(C10), 43.09 (N-CH_3) 63.87 (C7), 66.05 (C5), 88.96 (C-O of BOC), 84.55 (C-O of acid) 113.15 (C12), 113.44 (C14), 117.64 (C3), 118.33 (C2), 125.24 (C13), 125.48 (C16), 131.79 (C11), 133.14 (C15), 149.38 (C=O of BOC), 175.86 (C17). Positive ESIMS (m/z): 393.2 $[M+H]^+$ + 23(Na).

9,10-dihyrolysergic acid (6):-1N-BOC 9,10- dihyrolysergic acid (100 mg,2.70mmol) was dissolved under nitrogen in dry THF (10 mL) at room temp. A 1M solution of tetrabutyl ammonium fluoride (135mL, 1.35 mmol) in THF was added and stirred for 8h. After cooling to room tempetature,water (20mL) was added. After extraction with ethyl acetate (2x 20mL), the organic layers were washed with brine (10mL), dried over sodium sulphate and evaporated to yellow residue. The residue was purified by flash column chromatography (6 inchx 10mm x 20g) to give off white powder (48 mg, 56.2%), m.p. 267-268°C. IR (KBr, cm^{-1}): 3563, 3425, 3237, 3054, 3036, 2952, 2853, 2690, 2629, 2600, 2549, 2515, 1943, 1740, 1719, 1648, 1616, 1553, 1478, 1452, 1391, 1367, 1270, 1241, 1391, 1367, 1270, 1241, 1160, 1124, 1082, 1042, 991, 969, 937, 906, 837, 785, 749, 702, 654, 596, 578, 549, 516, 487. ^{1}H NMR(DMSO-d_6, 400 MHz, δppm):1.31-1.40(m, 1H, $H9_{ax}$), 2.62(m, 1H, $H7_{ax}$), 2.07(s, 3H, N-CH_3), 2.50-2.51 (m, 1H, $H4_{ax}$), 2.93-2.96(m, 3H, H10, H9eq, H8ax), 3.28(m, 1H, H7eq), 2.99-3.07(m, 1H, H4eq), 6.8-6.97(d, 1H, H2), 7.06-7.10(m, 2H, H13, H14), 7.21-7.23(d, 1H, H12).^{13}C NMR (DMSO-d_6, 100 MHz, δppm): 28.34(C4), 32.70(C9), 39.97(C8), 40.42(N-CH3), 56.90(C7), 64.98(C5), 107.12(C3), 109.53(C12), 112.59(C14), 119.41(C2), 122.32(C13), 125.15(C16), 129.46(C11), 133.06(C10), 170.45(C17).

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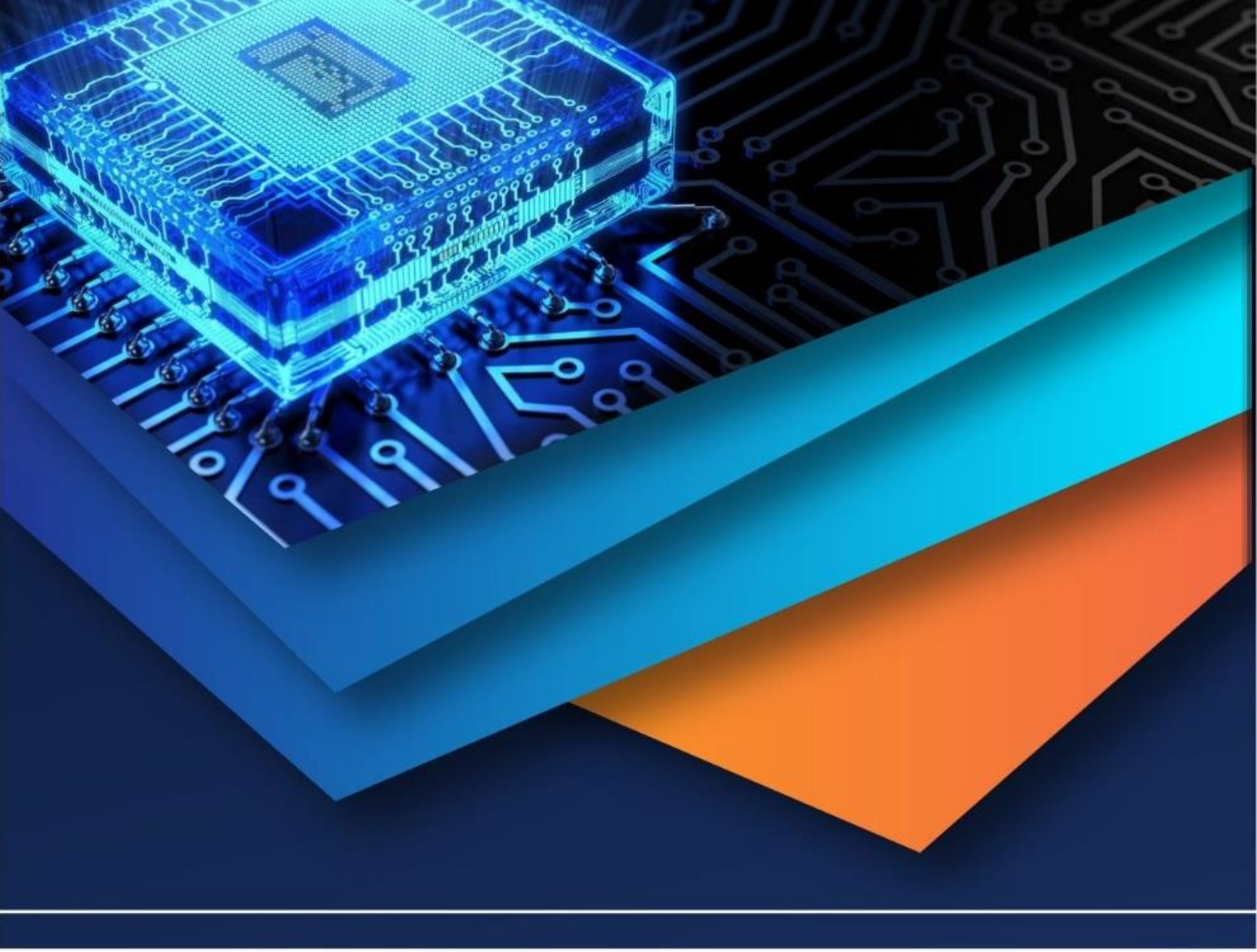

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