Phototransformations of 2-Benzylideindan-1-One Oximes: Synthesis of Indenoquinolines

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Abstract- *The photocyclization of substituted 2-benzylideneindan-1-one oximes yielded Indenoquinolines in 45-55% yield. The 2-benzylideneindan-1-one oximes were obtained by reacting 2-benzylideneindan-1-ones with NH2OH.HCl. Indanonewas treated with appropriately substituted benzaldehydes to afford 2-benzylideneindan-1-ones.*

Keywords- 2-Benzylideneindan-1-one oximes, indenoquinolines, indanone and benzaldehyde.

I. INTRODUCTION

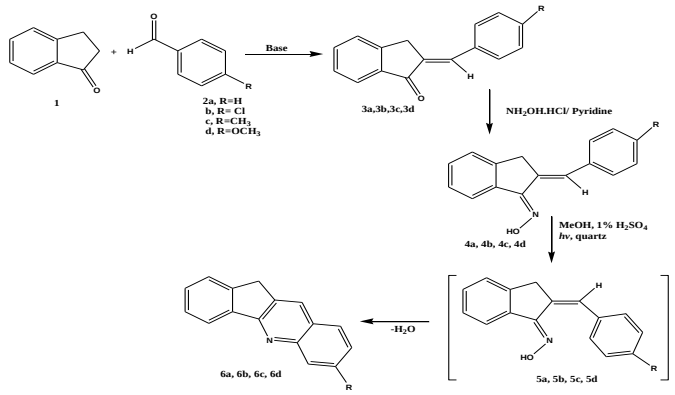
Tuberculosis (TB) is a contagious disease caused by Mycobacterium tuberculosis. It is a treatable infection which primarily affects the lungs causing an intense local inflammatory response that is critical to the pathogenesis of tuberculosis [1,2]. Despite availability of useful drugs TB continues to kill approximately 2 million people worldwide each year [3].

Recently, structure-based bio-evaluation of several new chemical entities against M. tuberculosis as pathogen has led to the identification of ring-substituted quinolines as a new structural class of anti-TB agents.The ring-substituted quinolines inhibit both drug-sensitive and drug-resistant M. tuberculosis in vitro. The structural optimization of ring-substituted quinolines to maximize anti-TB activity resulted in several promising analogs[4-9].

In view of the importance of quinolines and their derivatives in various fields of chemistry, biology and pharmacology, significant efforts have been devoted to their synthesis. Quinoline derivatives are reported to possess interesting pharmacological activities such as anti-plasmodial, anti-bacterial, anticarcinogenicand anti-proliferative activities [10-11]. Therefore, various methods such as the Skraup, Doebner – von Miller, Friedlääander and Combes procedures have been developed for the synthesis of quinoline derivatives[12-21].

Owing to the importance of quinolines, quinolinones, indenoquinolines and their derivatives the present synthetic studies have been carried outphotochemicallyfor indenoquinolines. The base catalysed condensation of indan-1-one with appropriately substituted benzaldehydes yielded the corresponding 2-benzylideneindan-1-ones [9].

These2-benzylideneindan-1-ones were subsequently treated with $NH_2OH.HCl$ in refluxing ethanolic pyridine to afford the corresponding 2-benzylideneindan-1-one oxime. Theoximes were then photocyclizedin acidic methanol to yield substituted Indenoquinolines.



Scheme 1: Photocatalysed synthesis of Indenoquinolines from 2-Benzylideindan-1-one oxime.

II. RESULTS AND DISCUSSION

The solution of 2-benzylideindan-1-one oxime**(4a)** in methanol containing 1% sulphuric acid was irradiated under nitrogen atmosphere with light from a 125 watts medium pressure mercury vapour lamp in a quartz vessel for 2.5h. The crude product was purified through column chromatography in toluene:petroleum ether (9:1) to give a yellow residue which on crystallization from chloroform- petroleum ether mixture gave 11*H*- indeno[1,2-*b*] quinoline**(6a)**, m.p. 162º-163ºC, in 55.0% yield. The structure of the product obtained was established through its IR, ^{1}H NMR and mass spectra. The most distinguishing feature of IR spectrum of the product **6a** was the absence of absorption peaks in the region 3500-3300cm^{-1} thereby implying that OH group originally present in the oxime**5a** has been eliminated. Instead it showed a

medium intensity peak at 1620-1600cm^{-1}presumably due to C=C and C=N stretch.The ^{1}H NMR spectra of **6a** showed that at the farthest end of the aromatic region at δ 8.30-8.33ppm was located a one proton doublet of a doublet (J=2.3 and 7.8 Hz) due to C_6-H. The deshielding of this proton is due to interaction with the lone pair of electrons on nitrogen atom.

Under similar conditions 7-chloro-11*H*- indeno[1,2-*b*] quinoline**(6b)** was obtained as a light yellow solid m.p. 196^o C, in 45.70% yield, from 2-(4'-chlorobenzylidene)indan-1-one oxime**(4b)**. The structure of the product **6b**obtained was established with IR, ^{1}H NMR and mass spectra. In the mass spectrum the most distinguishing feature of the product **6b** was the appearance of a molecular ion peak at m/z 251 (71.7%) along with the isotopic peak at m/z 253 (30.7%) thereby, indicating the presence of chlorine in the product **6b**.

Under similar conditions 7-methyl-11*H*- indeno[1,2-*b*] quinoline **(6c)**,a light yellow solid, m.p. 194^o, in 49.60% yield was obtained from 2-(4'-methylbenzylidene)indan-1-one oxime**(4c)**. The structure of the product obtained was established through its IR, ^{1}H NMR and mass spectra. In ^{1}H NMR spectra the most distinguishing feature of the product **6c** was appearance of two singlets at δ 2.59ppm and δ 4.05ppm in the aliphatic region. These peaks were due to C_7-CH_3 and C_{11}-CH_2 protons respectively.

Under similar conditionsphotochemical behaviour of 2-(4'-methoxybenzylidene)indan-1-one oxime**(4d)** was investigated. Here the usual chromatogragphic work up of the photolysate gave only one product i.e. *E*-2-(4'-methoxybenzylidene)indan-1-one **(3d)**, m.p. 138^{o}C, in 70% yield. The structure of compound **3d** was confirmed by its m.p. and also IR and ^{1}H NMR spectra.

III. EXPERIMENTAL

General: Melting points (°C) (m.p) were taken in open capillaries are uncorrected. IR spectra were recorded in Nujol mulls on a Perkin-EImer 842 spectrophotometer. Only principle absorption bands of interest are reported and expressed in cm^{-1}. H'-NMR spectra were recorded on Bruker AV-400 in $CDCl_3$. Chemical shifts are given in ppm relative to tetramethylsilane as an internal standard (δ= 0 ppm).Mass spectra were recorded at 70eV using a VG-70S instrument.

2-benzylideneindan-1-one oxime (4a): A mixture of E-2-benzylideneindan-1-one (**3a**, 2g), hydroxylamine hydrochloride (2g), pyridine (2ml) and ethanol (10ml) was refluxed on a water bath for 3h. Thereafter, the reaction mixture was poured into ice-cold water, acidified with dil. HCl and extracted with chloroform (2x25ml). The organic layer was washed with water (2x25ml) and then dried over anhydrous $CaCl_2$. Distillation of the solvent left a gummy mass, which was passed through column of silica gel. Elution of the column with toluene-petroleum ether mixture (6:4) yielded2-Benzylideneindan-1-one oxime**(4a)** as white crystals, m.p. 169°-171°C, yield 0.650g (31%).

IR (nujol, V max cm^{-1}):3380 (bs, O-H stretch), 1630 (m, >C=N stretch).

^{1}H NMR (400MHz, $CDCl_3$, δppm):4.02 (d, 2H, C_3-CH_2; J=2.0 Hz), 6.75 (t, l H, C_β-H, J= l.8Hz), 7.71-7.73 (m, 2H, $C_{2'}$-H, $C_{6'}$-H), 7.24-7.55 (m, 9H, C_4-H, C_5-H, C_6-H,$C_{3'}$-H, $C_{4'}$-H, $C_{5'}$-H), 8.56-8.59 (dd, lH, C_7-H. J=2.3 and 7.6 Hz), 10.98 (bs, 1H, OH, exchangeable with D_2O).
m/ z 255 (M+, 19.4%), 217 (100), 234 (77.4), 218 (95.1).

Following exactly the procedure as detailed for **(4a)**, 2-(4' substituted benzylidene)indan- 1-one oximes**(4b-4d)** were prepared.

2-(4'**-benzylideneindan-l-one oxime (4b):** White crystals from toluene: petroleum ether (6:4), m.p. 146, yield 21%.
IR (nujol, υ $_{max}$ cm^{-1}):3360 (br, O-H stretch), 1620 (m, >C=N stretch).

^{1}H NMR (400MHz, $CDCl_3$, δppm):3.98 (d, 2H, C_3-H, J =2.0 Hz), 6.80 (t, 1H, C_β-H, J=1.7 Hz), 7.75-7.78 (m, 2H, $C_{2'}$-H, $C_{6'}$-H), 7.25-7.47 (m, 6H, C_4-H, C_5-H, C_6-H, $C_{3'}$-H, $C_{4'}$-H, $C_{5'}$-H), 8.54- 8.57 (d, lH, C_7H. J= 7.62Hz), 11.14 (bs, lH, OH, exchangeable with D_2O).
m/z 271 ($M^{+\cdot}$+ 2, 28.6), 269 (M^+ 100), m/z 271 (28.6%).

E,Z-2-(4'**-methyl benzylideneindan-l-one oxime (4c):** White crystals from toluene: petroleum ether (6:4), m.p. 125°C, yield 16%.

IR (nujol, υ $_{max}$cm^{-1}): 3350 (br, O-H stretch),1620 (m, C= N stretch) .

^{1}H NMR (400MHz, $CDCl_3$, δppm): 2.36(s, 3H, $C_{4'}$ –CH_3), 3.99 (d, 2H, C_3-H; J =2.0Hz),
6.70 (t, 1H, C_β-H, J= I.8 Hz), 7.18-7.21 (d, 2H, $C_{3'}$-H, $C_{5'}$-H; J=8.0Hz), 7.30-7.41 (m, 3H, C_4-H, C_5-H, C_6-H), 7.60-7.63 (m, 2H, $C_{2'}$-H, $C_{6'}$-H), 8.53-8.55 (dd, IH, C_7H; J=7.68Hz and J=2.34Hz), 11.07 (bs, 1H , OH, exchangeable with D_2O) .
m/z 249 ($M^{+\cdot}$, 22.5), 248 (80.5), 232(100), 231 (74.3), 217 (31.7), 216 (35.2).

E,Z-2-(4'**-methoxy benzylideneindan-l-one oxime (4d):** White crystals from aqueous methanol, m.p. 130°C, yield 70%.

IR (nujol, υ_{max}cm^{-1}): 1680 (s, >C=O stretch in a five membered ring), 1620 (m, >C=C< stretch).
^{1}H NMR (400MHz, CDCl$_3$, δppm): 3.78 (s, 3H, $C_{4'}$-OCH_3), 4.00 (d, 2H, C_3-H, J=2.0Hz), 6.85-6.92 (d, 2H, $C_{3'}$-H, $C_{5'}$-H, J=8.1Hz), 7.24-7.45 (m, 6H, C_4-H, C_5-H, C_6-H,$C_{2'}$-H, $C_{6'}$-H =CH_β),8.35 (d, lH, C_7-H; J=8.0Hz).
m/z 250 ($M^{+\cdot}$ 100), 235 (19.1), 222 (15), 219 (18), 207 (53.5), 191 (13.2), 179 (45.3), 178 (64.2), 152 (24.9).

11*H*-indeno [1,2-*b*]quinoline (6a):2- benzylideneindan-l-one oxime (**4a**, 100mg,4.2mmol) was dissolved in dry methanol (100ml) by boiling for 2-3minand 2-3drops of H_2SO_4 were added to this solution. The solution was deoxygenated by bubbling nitrogen for 30min, and then irradiated in a quartz vessel with light from a 125 W medium pressure mercury vapour lamp under nitrogen atmosphere for a total of 2.5h. The progress of the reaction was monitored by TLC (toluene: petroleum ether 6:4). Thereafter, the reaction mixture was poured into ice-cold water and neutralized with ammonia solution. The resulting reaction mixture was washed twice with brine and then extracted with chloroform and finally dried over anhydrous $CaCl_2$.

The evaporation of solvent afforded a gummy residue, which was chromatographed over a column of silica gel (100-200 mesh). Elution of the column with toluene-petroleum ether mixture (6:4)gave a yellow solid which upon crystallisation from $CHCl_3$: petroleum ether mixture gave 11*H*-indeno [1,2-*b*]quinoline**(6a)** as light yellow crystals, m.p. 160^o-165^{o}C, yield 55%.

Following exactly the procedure as detailed for 11*H*-indeno [1,2-*b*]quinoline**(6b-6d)** were prepared.

IR (υ_{max}, cm^{-1}): 1620 (m, >C=N stretch),1600 (m, >C=C< stretch).

^{1}H NMR (CDCl$_3$, 400MHz , δppm): δ 4.06 (s, 2H, C11-CH_2), 7.48-7.55 (m, 3H, C_1-H, C_2-Hand C_3-H), 7.61-7.64 (m, 1H, C_8-H), 7.69-7.74 (dd, 1H, C_7-H, J=7.3 and7.6 Hz), 7.82-7.85 (d, 1H, C_9-H, J=8.0Hz), 8.20-8.22 (m, 2 H, C_4-H and C_{10}H), 8.20-8.33(dd , 1H, C_6-H, J=2.3 and 7. 8Hz)
m/z 217 ($M^{+\cdot}$, 100).

6-Chloro-11*H*-indeno[1,2-*b*]lquinoline (6b): Light yellow crystals, m. p. 196°C, yield 45.7%.

IR (υ_{max}, cm^{-1}): 1620 (m, >C=N stretch), 1600 (m, >C=C< stretch).

^{1}H NMR (CDCl$_3$, 400MHz , δppm): 4.04 (s, 2H, C_{11} -CH_2), 7.44 -7.48 (dd, 1H, C_8-H, J=2.2 and 8.4Hz), 7.50-7.54 (m, 2H, C_1-H and C_3-H), 7.59-7.63(m, 1H, C_2H), 7.74-7.77 (d, lH, C_9-H, J=8.0Hz) 8.16 (s, 1H, C_{10}-H), 8.20 (d, 1H, C_6-H, J=2.0Hz), 8.27-8.30 (dd, 1H, C_4-H, J=2.4 and 8.3Hz).
m/z 251 ($M^{+\cdot}$ 71.7), 253 (30.7), 216 (100).

6-Methyl-11*H*-indeno[1,2-*b*]quinoline (6c): Light yellow crytals, m.p. 194°C, yield 49.6%.

IR (υ_{max}, cm^{-1}): 1620 (m, C=N stretch), 1600 (m, C=C stretch).

^{1}H NMR (CDCl$_3$, 400MHz , δppm): 2.59 (s, 3H, C_7-H), 4.05 (s, 2H, C_{11}-CH_2) ,7.48-7.53 (m,3H, C_1-H, C_3-H, and C_8-H),7.60-7.63 (m, 1H, C_2-H),7.74 (d, 1H, C_9-H, J=7.8Hz),7.99 (s, 1H, C_{10}-H), 8.16 (d, 1H, C_6-H, J=2.7 Hz), 8.31 (dd, 1H, C_4-H, J=7.5Hz and 2.7Hz).
m/z 231 ($M^{+\cdot}$, 100), m/z 216 (35.1), m/z 202 (9.0).

2-(4'-methoxybenzylidene)indan-1-one oxime (5d): White crystals from aqueous methanolm.p. 138^{o}C, in 70% yield.
E-2-(4'-methoxybenzylidene)indan-1-one **(3d)**, m.p. 175-76°C, yield 8.6%

IR (υ_{max}, cm^{-1}): 1680 (s, >C=O stretch in a five membered ring),1620 (m, >C=C< stretch).

^{1}H NMR (CDCl$_3$, 400MHz ,δppm): 3.78 (s, 3H, $C_{4'}$-OCH_3), 4.0 ($C_{3'}$-H, $C_{5'}$-H, J=8.1Hz), 7.24-7.45 (m, 6H, C_4-H, C_5-H, C_6-H, $C_{2'}$-H, $C_{6'}$-H =CH_β), 8.35 (d, 1H, C_7-H, J=8.0 Hz).
m/z 250 ($M^{+\cdot}$, 100), 235 (19.1), 222 (15.0), 219 (18), 207 (53.5), 191 (13.2), 179 (45.3), 178 (64.2), 152 (24.9).

IV. CONCLUSION

In the present work 2-Benzylideindan-1-one oximes were substituted with different electron releasing and electron withdrawing groups to afford substituted Indenoquinolines, photochemically. Initially the oximes underwent photoisomerisation from E,E to E,Z isomer, which subsequently underwent photoelectrocyclization with simultaneous ground state dehydration of the putative N-hydroxyl intermediates to yield the Indenoquinolines. The IR, NMR and mass spectral studies revealed that all the substituted 2-Benzylideindan-1-one oximes were in E,E-configuration. The photocyclisation reaction yielded various Indenoquinolines in 45-55% yield.

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REFERENCES

[1] H.M. Scott, J.L. Flynn, Mycobacterium tuberculosis in chemokine receptor 2-deficient mice: Influence of dose on disease progression. Infect. Immun., vol. 70, pp. 5946–5954, 2002. [CrossRef] [PubMed].

[2] W. Peters, H.M. Scott, H.F. Chambers, J.L. Flynn, I.F. Charo, J.D. Ernst, Chemokine receptor 2 serves an early and essential role in resistance to Mycobacterium tuberculosis. Proc. Natl. Acad. Sci. USA vol. 98,pp. 7958–7963, 2001. [CrossRef] [PubMed]

[3] World Health Organization, Tuberculosis Fact Sheet, No. 104, 2006; please see: www.who.int/mediacentre/factsheets/ fs104/en/.

[4] S. Vangapandu, M. Jain, R. Jain, S. Kaur, P. P. Singh, Bioorg. "Ring-substituted quinolines as potential anti-tuberculosis agents", Med. Chem. vol. 12, pp. 2501, 2004.

[5] B. Vaitilingam, A.Nayyar, P. B. Palde, V. Monga, R. Jain, S. Kaur, P. P. Singh, "Synthesis and antimycobacterial activities of ring-substituted quinolinecarboxylic acid/ester analogues. Part 1", Bioorg. Med. Chem. vol. 12, pp. 4179, 2004.

[6] V. Monga, A. Nayyar, B. Vaitilingam, P. B. Palde, S. S. Jhamb, S. Kaur, P. P. Singh, R. Jain, "Ring-substituted quinolines. Part 2: Synthesis and antimycobacterial activities of ring-substituted quinolinecarbohydrazide and ring-substituted quinolinecarboxamide analogues",Bioorg. Med. Chem. vol. 12, pp. 6465, 2004.

[7] A. Nayyar, R. Jain, "Synthesis and anti-tuberculosis activity of 2, 4-disubstituted quinolones", Indian Journal of Chemistry vol. 47, pp.117-128, 2008.

[8] S. Damavandi, R. Sandaroos, "Solvent-free one pot synthesis of indenoquinolinonescatalyzed by iron(III) triflate", Heterocycl. Commun., Vol. 17(3-4), pp. 121–124, 2011.

[9] N. G.Khaligh, "Three-component, one-pot synthesis of benzo[f]indenoquinoline derivativescatalyzed by poly(4-vinylpyridinium) hydrogen sulphate", Polycyclic Aromatic Compounds, vol. 35, pp. 428–438, 2015.

[10] D. E., Bierer, , L. G. Dubenko, P. Zhang, Q. Lu, P. A. Imbach, A. W. Garofalo, P. W. Phuan, D. M. Fort, J. Litvak, R. E. Geber, B. Sloan, R. Cooper, and G. M. Reaven. "Antihyperglycemic Activities of Cryptolepine Analogues: An Ethnobotanical Lead Structure Isolated from Cryptolepissanguinolenta." Journal of Medicinal Chemistry vol. 41 pp. 2754–2764, 1998.

[11] J. R. Brooks, D. Berman, M. S. Glitzer, L. R. Gordon, R. L. Primka, G. F. Reynolds, and G. H. Rasmusson. "Effect of a New 5 Alpha-Reductase Inhibitor on Size, Histologic Characteristics, and Androgen Concentrations of the Canine Prostate." The Prostate,vol. 3,pp. 35–44, 1982.

[12] M. Yamato, Y. Takeuchi, K. Hashigaki, Y. Ikeda, C. Ming-rong, K. Takeuchi, M. Matsushima, T. Tsuruo, T. Tashiro, S. Tsukagoshi, Y. Yamashita, and H. Nakano. "Synthesis and Antitumor Activity of Fused Tetracyclic Quinoline Derivatives. 1." Journal of Medicinal Chemistry vol. 32 pp. 1295–1300, 1989.

[13] A. Rampa, A. Bisi, F. Belluti, S. Gobbi, P. Valenti, V. Andrisano, V. Cavrini, A. Cavalli, and M. Recanatini. "Acetylcholinesterase Inhibitors for Potential Use in Alzheimer's Disease: Molecular Modeling, Synthesis and Kinetic Evaluation of 11Hindeno-[1,2-*b*]-quinolin-10-ylamine Derivatives." Bioorganic & Medicinal Chemistry vol. 8,pp. 497–506, 2000.

[14] L. W. Deady, J. Desneves, A. J. Kaye, G. J. Finlay, B. C. Baguley, and W. A. Denny. "Positioning of the Carboxamide Side Chain in 11-Oxo-11H-indeno[1,2-*b*]quinolinecarboxamide Anticancer Agents: Effects on Cytotoxicity." Bioorganic & Medicinal Chemistry vol. 9 pp. 445–452, 2001.

[15] X. Bu and L. W. Deady. "A Preparation of Methyl 2-amino-3-formylbenzoate and its Use in Friedlander Synthesis." Synthetic Communications vol. 29, pp. 4223–4233, 1999.

[16] C. S. Cho, B. T. Kim, H. J. Choi, T. J. Kim, and S. C. Shim. "Ruthenium-Catalyzed Oxidative Coupling and Cyclization between 2-aminobenzyl Alcohol and Secondary Alcohols Leading to Quinolines." Tetrahedron vol. 59, pp. 7997–8002, 2003.

[17] T. Sunami, K. Nishio, F. Kanzawa, K. Fukuoka, S. Kudoh, J. Yoshikawa, and N. Saijo. "Combination Effects of TAS-103, A Novel Dual Topoisomerase I and II Inhibitor, with Other Anticancer Agents on Human Small Cell Lung Cancer Cells." Cancer Chemotherapy and Pharmacology vol. 43, 394–401, 1999.

[18] G. J. Atwell, G. W. Rewcastle, B. C. Baguley, and W. A. Denny. "Potential Antitumor Agents. 50. In vivo Solid-Tumor Activity of Derivatives of N-[2-(dimethylamino)ethyl]acridine-4-carboxamide." Journal of Medicinal Chemistry vol. 30,pp. 664–669, 1987.

[19] J. A. Spicer, S. A. Gamage, G. J. Atwell, G. F. Finlay, B. C. Baguley, and W. A. Denny. "Structure−Activity Relationships for Acridine Substituted Analogues of the Mixed Topoisomerase I/II Inhibitor N-[2-(Dimethylamino)ethyl]acridine-4- carboxamide." Journal of Medicinal Chemistry, vol. 40,pp. 1919–1929, 1997.

[20] G. Kohlhagen, K. Paull, M. Cushman, P. Nagafuji, and Y. Pommier. "ProteinLinked DNA Strand Breaks Induced by NSC 314622, a Novel Noncamptothecin Topoisomerase I Poison." Molecular Pharmacology vol. 54, pp. 50–58, 1998.

[21] S. Antony, M. Jayaraman, G. Laco, G. Kohlhagen, K. W. Kohn, M. Cushman, and Y. Pommier, "Differential Induction of Topoisomerase I-DNA Cleavage Complexes by the Indenoisoquinoline MJ-III-65 (NSC 706744) and Camptothecin: Base Sequence Analysis and Activity against Camptothecin-Resistant Topoisomerases I." Cancer Research vol. 63, pp. 7428–7435, 2003.