Tetrahedron Letters No.13, pp. 1027-1030, 1969. Pergamon Press. Printed in Great Britain.

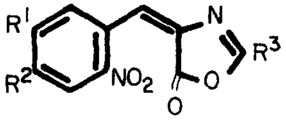
NOVEL SYNTHESIS OF QUINOLINE DERIVATIVES WITH TRIETHYL PHOSPHITE

T. Kametani, K. Nyu, T. Yamanaka, H. Yagi, and K. Ogasawara
Pharmaceutical Institute, School of Medicine,
Tohoku University, No. 85, Kitayobancho, Sendai, Japan

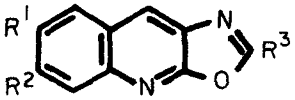
(Received in Japan 25 January 1969; received in UK for publication 10 February 1969)

The reaction of aromatic nitro compounds with triethyl phosphite has hitherto been investigated by many researchers[1-14]. Among them, Sundberg, *et al.*[4] reported that deoxygenation of 2-nitrostyrenes by triethyl phosphite gave the indole derivatives. In this case the nitro group is assumed to react predominantly with double bond. On the other hand, we have reported that the compound (I), whose carbonyl and 2-nitrophenyl groups were in relation to *cis* conformation each other, was reacted with triethyl phosphite to give the quinoline derivative (II) in good yield[7]. Hereby we wish to report the novel synthesis of quinoline derivative by treatment of ethyl 2-nitrobenzylidenemalonates (III) and (IV), whose 2-nitrophenyl groups are presented against one of two carbonyl groups with *cis* conformation, with triethyl phosphite.

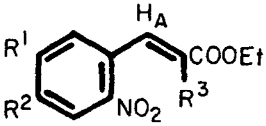
Treatment of ethyl 4,5-dimethoxy-2-nitrobenzylidenemalonate (III) (1 mol.) and ethyl 4-benzyloxy-5-methoxy-2-nitrobenzylidenemalonate (IV) (1 mol.) with triethyl phosphite (5 mol.) at 160 - 170° for 20 hr. in a current of nitrogen afforded the 2-ethoxy-3-ethoxycarbonyl-6,7-dimethoxyquinoline (V) (61 %), m.p. 91 - 94°, $\nu_{max.}$ (in $CHCl_3$) 1718 (ester C=O), 1627 $cm.^{-1}$ (C=N-), δ (p.p.m.) (in $CDCl_3$) 1.40, 1.47 (each 3H, 2t, $\underline{J}$ 7 c./sec., 2 x $CH_2C\underline{H}_3$), 3.96, 4.01 (each 3H, 2s, 2 x $OC\underline{H}_3$), 4.38, 4.55 (each 2H, 2q, $\underline{J}$ 7 c./sec., 2 x $-C\underline{H}_2CH_3$), 7.00 (1H, s, C_5-H), 7.14 (1H, s, C_8-H), 8.45 (1H, s, C_4-H), and 7-benzyloxy-2-ethoxy-3-ethoxycarbonyl-6-methoxyquinoline (VI) (68 %), m.p. 95 - 98°, $\nu_{max.}$ (in $CHCl_3$) 1711 (ester C=O), 1620 $cm.^{-1}$ (C=N-), δ (p.p.m.) (in $CDCl_3$) 1.41, 1.47 (each 3H, 2t, $\underline{J}$ 6.6 c./sec., 2 x $-CH_2C\underline{H}_3$), 3.96 (3H, s, $OC\underline{H}_3$), 4.38, 4.54 (each 2H, 2q, $\underline{J}$ 6.6 c./sec., 2 X $-C\underline{H}_2CH_3$), 5.28 (2H, s, benzylic protons), 7.04 (1H, s, C_8-H), 7.16 - 7.56 (6H, m, C_5-H and phenyl aromatic protons), 8.47 (1H, s, C_4-H).



(I)



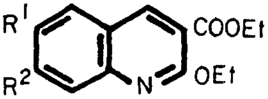
(II)



(III) $R^1 = R^2 = OMe$, $R^3 = COOEt$

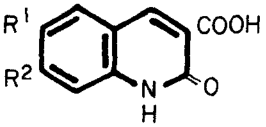
(IV) $R^1 = OMe$, $R^2 = OCH_2Ph$, $R^3 = COOEt$

(IX) $R^1 = OMe$, $R^2 = OCH_2Ph$, $R^3 = H_B$



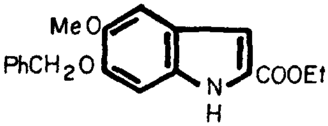
(V) $R^1 = R^2 = OMe$

(VI) $R^1 = OMe$, $R^2 = OCH_2Ph$



(VII) $R^1 = R^2 = OMe$

(VIII) $R^1 = OMe$, $R^2 = OCH_2Ph$



(X)

Hydrolysis of the above compounds, (V) and (VI), with hydrochloric acid gave the corresponding quinolone derivatives, (VII) (96 %), m.p. > 270°, $\nu_{max.}$ (KBr) 1710 (acid C=O), 1650 $cm.^{-1}$ (lactam C=O), δ (p.p.m.) (in CF_3CO_2H) 4.13, 4.19 (each 3H, 2s, 2 x $OC\underline{H}_3$), 7.39, 7.49 (each 1H, s, aromatic protons), 9.32 (1H, s, C_4-H), and (VIII) (51 %), m.p. > 280°, $\nu_{max.}$ (in KBr) 1725 (acid C=O), 1655 $cm.^{-1}$ (lactam C=O), δ (p.p.m.) (in CF_3CO_2H) 4.10 (3H, s, $OC\underline{H}_3$), 5.40 (2H, s, benzylic protons), 7.25, 7.40 (each 1H, 2s, aromatic protons), 7.45 (5H, s, phenyl aromatic protons), 9.25 (1H, s, C_4-H), respectively.

On the other hand, the same treatment of ethyl 4-benzyloxy-3-methoxy-2-nitrocinnamate (IX) [δ (p.p.m.) 8.11 (1H, $\underline{J}$ 16 c./sec., H_A), 6.12 (1H, $\underline{J}$ 16 c./sec., H_B); this fact proves the <u>trans</u>-conformation] with trithyl phosphite gave the 6-benzyloxy-2-ethoxycarbonyl-5-methoxyindole (X) (56 %), m.p. 135 - 136°, $\nu_{max.}$ (in $CHCl_3$) 3400 (NH), 1688 (ester C=O), 1630 $cm.^{-1}$ (C=C), δ (p.p.m.) (in $CDCl_3$) 1.38 (3H, t, $\underline{J}$ 6.5 c./sec., $-CH_2C\underline{H}_3$), 3.91 (3H, s, $OC\underline{H}_3$), 4.35 (2H, q, $\underline{J}$ 6.5 c./sec., $-C\underline{H}_2CH_3$), 5.16 (2H, s, benzylic protons), 6.82 (1H, s, C_3-H), 7.05 (2H, broad s, C_4- and C_7-H), 7.35 (5H, broad s, phenyl aromatic protons), 8.95 (1H, broad s, NH).

This fact is in accord with that of Sundberg's data. Namely, when both 2-nitrophenyl and carbonyl groups were in relation to <u>trans</u> conformation, the formation of the indole has been proved, whereas the compounds with the reverse conformation as III and IV afforded our expected quinoline derivatives. Thus this work provides the novel synthesis of quinoline derivatives having various substituents.

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