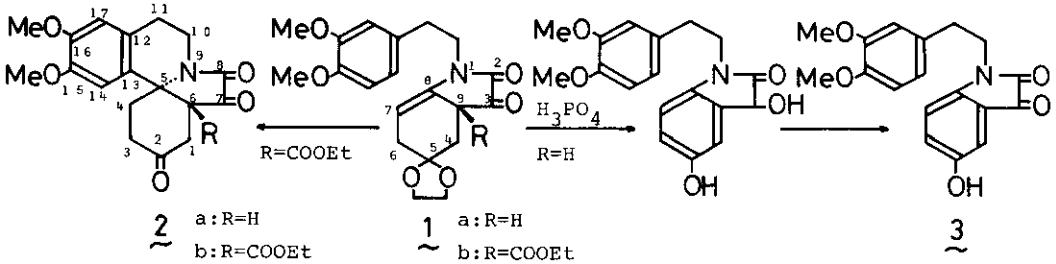
A NOVEL REARRANGEMENT OF AN 6-ETHOXYCARBONYL-2,7,8-TRIOXOERYTHRINAN TO AN ISOQUINOLINO-α-PYRIDONE DERIVATIVE[1]

Yoshisuke Tsuda* and Yuki Sakai
Faculty of Pharmaceutical Sciences, Kanazawa University, Kanazawa 920, Japan
Takehiro Sano
Showa College of Pharmaceutical Sciences, Setagaya-ku, Tokyo 154, Japan

Acid catalysed cyclization of the dioxopyrroline derivative 1b smoothly gave the 2-oxoerthrinan derivative 2b after deacetalization of the intermediate 5. Further acid treatment of 2b gave the pentacyclic compound 7 which could rearrange into an isoquinolino-α-pyridone derivative 13 on additional treatment with anhyd. H_3PO_4 or PPA. Each compound, 5, 2b, 7, or 13, was isolable in a satisfactory yield by controlling the reaction condition.

In a previous paper[2] we showed high yield cyclization of 9-ethoxycarbonyl-1-β-arylethyl-tetrahydroisatins to 6-ethoxycarbonyl-7,8-dioxoerythrinans. A particular advantage in the use of an 9-ethoxycarbonyl derivative rather than that of an 1-β-arylethyl-tetrahydroisatin itself may be in the synthesis of an oxoerythrinan such as 2, because attempted cyclization of 1a failed to yield the corresponding erythrinan 2a; aromatization took place to furnish a hydroxyisatin 3[3] instead.

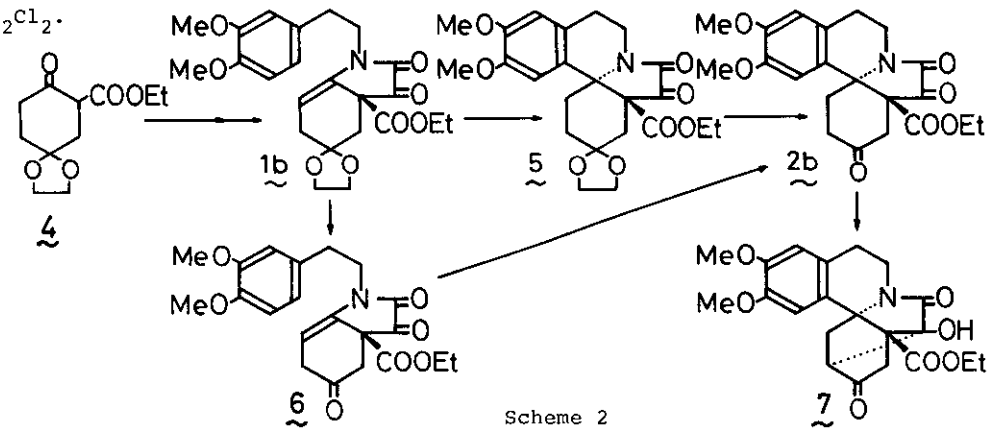
In this communication we show easy cyclization of the ethoxycarbonyl derivative 1b to the corresponding erythrinan 2b, which is smoothly convertible to 2a by decarbethoxylation with $MgCl_2$-DMSO[4], and describe a new rearrangement of 2b to an isoquinolino-α-pyridone derivative 13.



2 a:R=H b:R=COOEt 1 a:R=H b:R=COOEt 3

Scheme 1

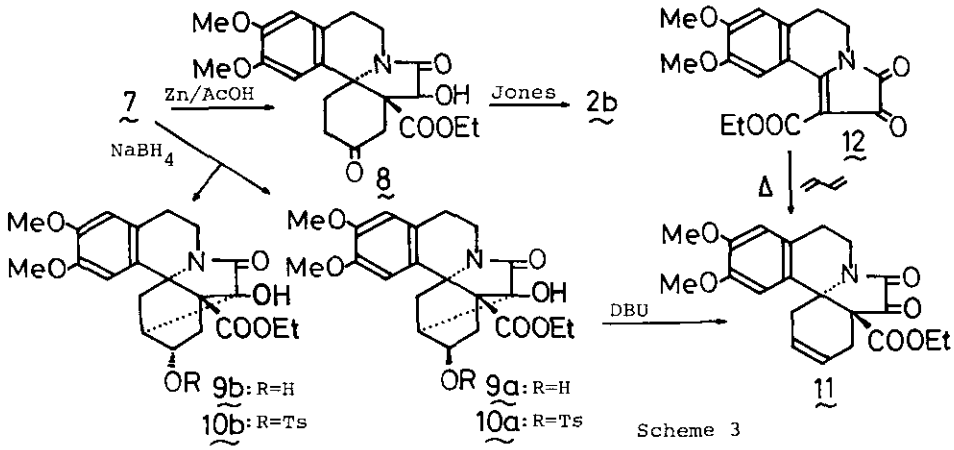
The dioxopyrroline 1b was easily prepared by condensation of 4[6] with homoveratrylamine followed by oxalylation as described previously[2]. Treatment of 1b with $AgClO_4$ in benzene at 90° for 1 hr yielded 5[5], 2b[5], and 7[5] in 25, 32, and 25% yields, respectively. Reaction of 1b with $BF_3 \cdot Et_2O$ in CH_2Cl_2 under reflux for 40 min gave a similar result, ratios of 5, 2b, and 7 being ca. 1:1:1. On the other hand, treatment of 1b with anhyd. H_3PO_4 at room temp. for 1.5 hr produced, together with 7 (10%), the deacetalization product 6 (70%) which, on further treatment at 70° with the same reagent, was smoothly converted to 7. The compound 7 was also obtained in high yield from 2b on treatment with excess $BF_3 \cdot Et_2O$ in CH_2Cl_2.



Scheme 2

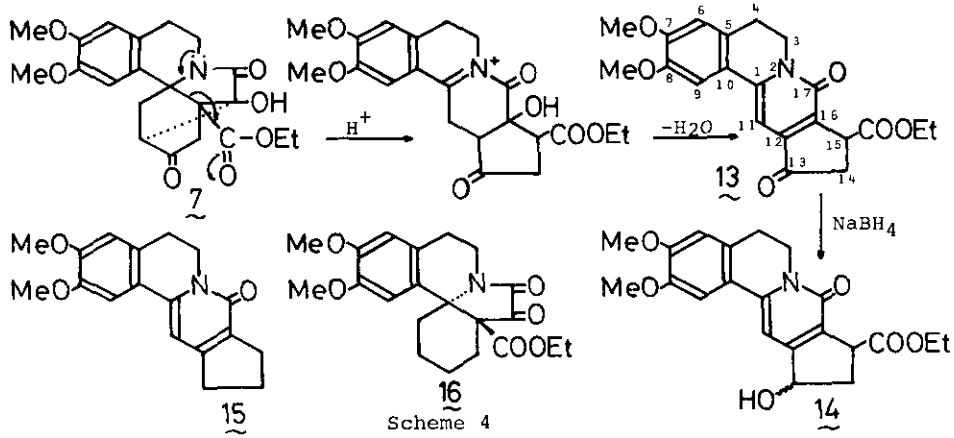
The structure of 5, 6, and 2b are based on the spectroscopic evidences and usual interconversions. The compound 7 was suggested as the pentacyclic ketol having resulted from an intramolecular aldol condensation of 2b, since it exhibited ^{13}C-NMR signals of three $-\overset{|}{C}-$ (δ 65.9, 68.6, and 88.2) and one $-\overset{|}{C}H$ (δ 54.2), and the IR absorptions of a 5-membered ring ketone(1760), an ester(1715), a lactam (1695), and a hydroxyl group(3400 br cm^{-1}). This assignment was verified by the following reactions.

Zn-AcOH reduction of 7 yielded a mixture of the keto-alcohol (8) which on Jones oxidation furnished a trioxo-compound identical with 2b in all respects (IR, TLC, and mp). $NaBH_4$ reduction of 7 afforded a mixture of the epimeric alcohols(9a and 9b) which was tosylated and the resulting mixture of the tosylates was treated with DBU in benzene for 5 min at 80°. Thus the β-tosylate (10a)[5] was changed into the olefin (11)[5], and the α-tosylate (10b)[5] remained unchanged. Identity of the olefin with the Diels-Alder product (11) of isoquinolinopyrrolinedione (12) and butadiene was confirmed by direct comparisons (mp, TLC, IR, and NMR).



Scheme 3

Treatment of the compound 7 with anhyd. H_3PO_4 or PPA at 70-100° produced a new compound, yellow prisms, mp 182-183°, $C_{21}H_{21}NO_6$, UV(EtOH): λ_{max} (ε) nm 286 (15600), 303sh(13900), 380(15000). IR(KBr): 1720, 1653, 1605cm^{-1}. ^{1}H-NMR($CDCl_3$): δ 7.21(1H,s), 6.82(1H,s), 6.76(1H,s), 4.26(2H,q,J=7 Hz), 3.95(6H,s), 1.32(3H,t,J=7 Hz). ^{13}C-NMR($CDCl_3$): δ 204.7s, 172.3s, 160.7s, 151.4s, 148.7s, 145.5s, 144.7s, 141.5s, 128.9s, 121.4s, 110.3d, 108.2d, 94.0d, 61.6t, 56.3q, 56.1q, 41.7d, 41.0t, 39.9t, 27.5t, 14.1q. The same compound was obtained directly from 1b on heating with anhyd. H_3PO_4 at 100° for 1.5 hr. The spectral data indicated that the compound is an isoquinolino-α-pyridone 13. The assigned structure was supported by the UV spectrum of the alcohol 14[5] (λ_{max} 269 and 348 nm) derived from 13 by $NaBH_4$ reduction which was similar to that reported for 15 (λ_{max} 267 and 343 nm)[8].



Scheme 4

The formation of 13 from the 2,7,8-trioxoerythrinan derivative 2b, through the intramolecular aldol product 7, is well explained as shown in Scheme 4: 5,6-bond cleavage of 7 by retro-Mannich reaction followed by dehydration gives 13 without

any difficulty. Supporting this mechanism, the erythrinan 16[2] was found to be stable to anhyd. H_3PO_4 at 100°.

Acknowledgement A part of this work was supported by Grant-in-Aid for Special Project Research, Chemical Research in Development and Utilization of Nitrogen-Organic Resources, from the Ministry of Education, Science and Culture, for which one of the author (Y. T.) expresses his appreciation.

References and Notes

1. Dioxopyrrolines XIV. Syntheses of Erythrina and Related Alkaloids(2). Part XIII: see ref. 2).
2. Syntheses of Erythrina and Related Alkaloids(1): Y. Tsuda, Y. Sakai, M. Kaneko, Y. Ishiguro, K. Isobe, J. Taga, and T. Sano, Heterocycles, 15
3. A. Mondon, K. F. Hansen, K. Boehme, H. P. Faro, H. J. Nestler, H. G. Vilhuber, and K. Böttcher, Chem. Ber., 103, 615(1970).
4. Y. Tsuda and Y. Sakai, Synthesis, in press.
5. 1b. mp 106-107°, yellow prisms. IR(KBr): 1770,1720, 1690cm^{-1}. ^{1}H-NMR($CDCl_3$):δ 6.80(3H,s,ArH), 5.20(1H,t,J=4Hz,-CH=), 3.9-4.0(4H,ethyleneketal), 4.09(2H,q,J=7Hz,$COOCH_2CH_3$), 3.82, 3.80(each 3H,s,OCH_3), 1.24(3H,t,J=7Hz,$COOCH_2CH_3$).
5. mp 185-186°. IR(KBr): 1765, 1735, 1710cm^{-1}. ^{1}H-NMR($CDCl_3$): δ 6.55(2H,s,ArH), 3.88(4H,s,ethyleneketal), 3.81(6H,s,OCH_3 x 2), 3.57(2H,q,J=7Hz,$COOCH_2CH_3$), 0.68 (3H,t,J=7Hz,$COOCH_2CH_3$).
6. gum. ^{1}H-NMR($CDCl_3$):δ6.70(3H,s,ArH), 5.28(1H,t,J=5Hz,-CH=), (2H,q,J=7Hz, $COOCH_2CH_3$), 3.81, 3.78(each 3H,s,OCH_3),1.13(3H,t,J=7Hz,$COOCH_2CH_3$).
2b. mp 282-283°. IR(KBr): 1770,1742, 1720, 1703cm^{-1}. ^{1}H-NMR($CDCl_3$):δ 6.62, 6.56 (each 1H,s,ArH), 3.87, 3.86(each 3H,s,OCH_3), 3.66(2H,qd,J=7,1.5Hz,$COOCH_2CH_3$), 3.32(2H,s,-$COCH_2$-), 0.73(3H,t,J=7Hz,$COOCH_2CH_3$).
7. mp 279-282°(decomp.). IR(KBr): 1760, 1715, 1695cm^{-1}. ^{1}H-NMR($CDCl_3$): δ 6.75, 6.67(each 1H,s,ArH), 4.01(2H,q,J=7Hz,$COOCH_2CH_3$). 3,89, 3.88(each 3H,s,OCH_3), 0.94(3H,t,J=7Hz,$COOCH_2CH_3$). ^{13}C-NMR($CDCl_3$): δ 207.1s, 169.1s, 168.2s, 149.2s, 148.4s, 128.1s, 122.8s, 112.1d, 108.7d, 88.2s, 68.6s, 65.9s, 61.3t, 56.5q, 56.0 q, 54.2d, 39.2t, 36.7t, 34.9t, 28.7t, 13.8q.
9a + 9b. gum. IR($CHCl_3$): 1715cm^{-1}. ^{1}H-NMR($CDCl_3$): ArH 7.03(0.5H), 6.72(0.5H), 6.58(1H).
10a. ^{1}H-NMR($CDCl_3$):δ7.70,7.25(each 2H,d,J=8Hz,Ts), 6.83,6.52(each 1H,s,ArH).
10b. ^{1}H-NMR($CDCl_3$):δ7.77,7.26(each 2H,d,J=8Hz,Ts), 6.61,6.54(each 1H,s,ArH).
11. mp 176-180°, pale yellow prisms. IR(KBr):1765, 1730, 1715cm^{-1}.^{1}H-NMR($CDCl_3$):δ 6.63,6.52(each 1H,s,ArH), 6.2-5.6(2H,-CH=CH-), 3.80(6H,s,OCH_3 x 2), 3.57(2H,q, J=7Hz,$COOCH_2CH_3$),0.67(3H,t,J=7Hz,$COOCH_2CH_3$).
14. mp 199-201°. UVλ_{max}(ε) in EtOH: 269(9000),348(24800). IR(KBr): 1720,1655, 1608,1595cm^{-1}. ^{1}H-NMR($CDCl_3$): δ 7.21,6.80,6.73(each 1H,s,ArH),4.95-5.15(1H,>CH-OH), 4.25(2H,q,J=7Hz,$COOCH_2CH_3$), 3.95,3.94(each 3H,s,OCH_3), 3.57(1H,d,J=11Hz,-OH), 1.34(3H,t,J=7Hz,$COOCH_2CH_3$).
6. cf. R.M.Lukes, G.I.Poos, and L.H.Sarett, J. Am. Chem. Soc., 40, 1401(1952).
7. T. Sano, J. Toda, and Y. Tsuda, unpublished result.
8. A. Mondon, E. Oelrich, and R.Schickfluss, Chem. Ber., 105, 2036(1972).

Received, 6th October, 1980