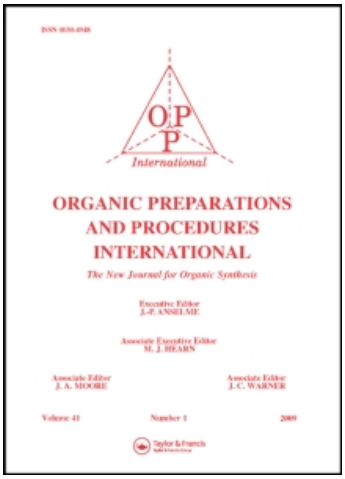


Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

AN EFFICIENT ROUTE TO XANTHOBILIRUBIC ACID, AN OXODIPYRRYLMETHENE

J. O. Grunewald[a]; R. Cullen[a]; J. Bredfeldt[a]; E. R. Strope[a]
[a] Department of Biochemistry, University of Kansas Medical Center, Kansas City, Kansas

To cite this Article Grunewald, J. O. , Cullen, R. , Bredfeldt, J. and Strope, E. R.(1975) 'AN EFFICIENT ROUTE TO XANTHOBILIRUBIC ACID, AN OXODIPYRRYLMETHENE', Organic Preparations and Procedures International, 7: 3, 103 — 110
To link to this Article: DOI: 10.1080/00304947509355128
URL: http://dx.doi.org/10.1080/00304947509355128

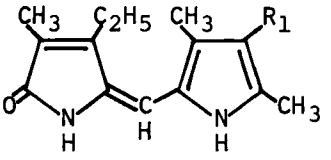
ORGANIC PREPARATIONS AND PROCEDURES INT. 7(3), 103-110 (1975)

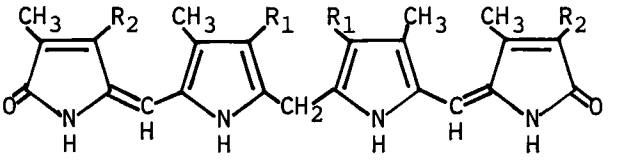
AN EFFICIENT ROUTE TO XANTHOBILIRUBIC ACID, AN OXODIPYRRYLMETHENE[1]

J. O. Grunewald*, R. Cullen, J. Bredfeldt and E. R. Strope

Department of Biochemistry
University of Kansas Medical Center
Kansas City, Kansas 66103

Although the monumental work of Fischer and his colleagues[2] still serves as the primary reference to synthetic procedures for monopyrroles and pyrrole pigments, some of the methods for the preparation of moderately complex molecules are tedious and require many steps. Additionally some of Fischer's improvements on his earlier work are difficult to locate in the literature. We report here a more efficient route to xanthobilirubic acid (Ia, 5-[(1,5-dihydro-3-ethyl-4-methyl-5-oxo-2H-pyrrol-2-ylidene)methyl]-2,4-dimethyl-1H-pyrrole-3-propanoic acid), using modified literature procedures. Oxodipyrrylmethenes such as Ia are useful as model compounds for bilirubin (II) in photooxidation studies,[3] an area of intense research interest[4] because of the use of phototherapy in neonatal jaundice.[5]



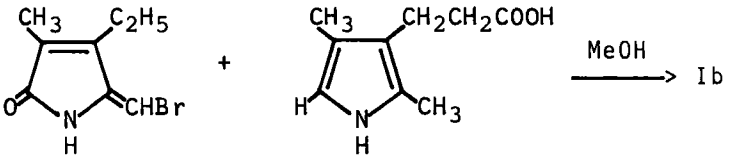


Ia R_1 = CH_2CH_2COOH

Ib R_1 = $CH_2CH_2COOCH_3$

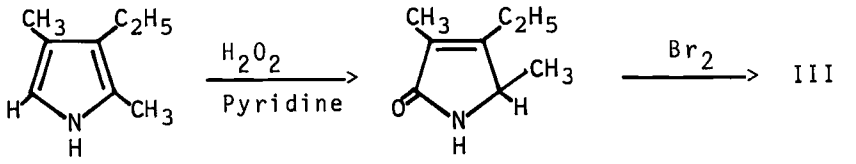
II R_1 = CH_2CH_2COOH
R_2 = $CH{=}CH_2$

The key step in the synthesis of Ia is the condensation of 2-bromomethylene-3-ethyl-4-methyl-3-pyrrolin-5-one (III) with 2,4-dimethyl-1H-pyrrole-3-propanoic acid (IV), [6-8] which proceeds in reasonable yield to



III IV

give the methyl ester Ib. The problem lies in obtaining the monopyrrolic reactants in satisfactory yields and purity. The two-step synthesis of III involves reaction of 2,4-dimethyl-3-ethyl-1H-pyrrole (kryptopyrrole, V)[9] with hydrogen peroxide, then bromination of the product, 4-ethyl-3,5-dimethyl-3-pyrrolin-2-one (VI). Fischer's original procedure[7] (0.5 mole bromine/mole VI) gave only trace amounts of III in an intractable mixture.



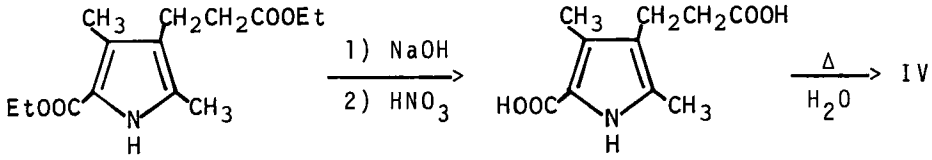
V VI

Only when a later modified procedure was found[8] (1.8 mole bromine/mole VI) was III obtained in good yield.

Both of the methods developed by Fischer for the synthesis of 2,4-dimethyl-1H-pyrrole-3-propanoic acid (IV)[10] required five steps and utilized ethyl 3,5-dimethyl-1H-pyrrole-2-carboxylate (VII) as starting material. One route employed hydrogen cyanide[11] and the other required diethyl methoxymethylmalonate, the synthesis of which involves the use

of the carcinogen, chloromethyl methyl ether.[12] Additionally compound VII itself is not available commercially and must be prepared in two steps[13] from diethyl 3,5-dimethyl-1H-pyrrole-2,4-dicarboxylate (VIII).[9]

We therefore sought a more convenient synthesis for IV; thus we prepared ethyl 4-(2-ethoxycarbonylethyl)-3,5-dimethyl-1H-pyrrole-2-carboxylate (IX) according to the simple two-step procedure of Bullock et al.[14] using the readily available starting materials 2,4-pentanedione, ethyl acrylate and ethyl acetoacetate. The hydrolysis of IX to the diacid X proceeded in near quantitative yield when nitric instead of sulfuric acid



IX X

was used to neutralize the hydrolysis mixture, so that only a small amount of water was necessary to wash the inorganic salt away from the product (X is quite soluble in water). The unpurified diacid X was decarboxylated by heating it in water;[15] extraction with ether gave IV in 75-85% yield. Since IV is rapidly oxidized in air, all possible manipulations were carried out under nitrogen.

We modified Fischer's condensation procedure[7,8] by using purified III and the free acid rather than its methyl ester and by carrying out the reaction under nitrogen to prevent oxidation of IV and the product. The pure methyl ester Ib is obtained (esterified by the solvent, liberated HBr as catalyst) in greater than fifty percent yield after recrystallization from benzene.

Alkaline hydrolysis of Ib was carried out under nitrogen, with the reaction mixture protected from light. The intermediate sodium salt was

isolated, then neutralized to give Ia in greater than seventy-five percent yield. Xanthobilirubic acid Ia so obtained was homogenous by tlc and spectral criteria and was used without further purification in photochemical experiments.[3] Recrystallization from pyridine[6] was unnecessary.

EXPERIMENTAL

Melting points were determined on a Fisher-Johns apparatus and are uncorrected. Ir spectra were recorded on a Beckman Model IR-8 grating spectrometer, nmr spectra on a Varian T-60, with tetramethylsilane as internal standard, and uv-visible spectra on a Cary Model 14 recording spectrophotometer. Mass spectra were run on an Atlas CH-5 spectrometer, using a direct inlet system.

2-Bromomethylene-3-ethyl-4-methyl-3-pyrrolin-5-one (III)[8].- 4-Ethyl-3,5-dimethyl-3-pyrrolin-2-one (VI, 19.5 g, 0.14 mol)[7,8] was dissolved in 39 ml absolute methanol,[16] and the solution, protected with a drying tube, was brought to reflux. A solution of bromine (12.7 ml, 39.5 g, 0.247 mol) in 66 ml absolute methanol was then added all at once, and the reaction mixture refluxed for 6 hr. The methanol was removed in vacuo and the residue placed in a vacuum desiccator with solid NaOH overnight. Recrystallization of the dark brown residue from ethanol-water followed by sublimation (100°, 50 μ) yielded 16.30 g (54%) of white crystals, mp. 139-141°, lit.[8] mp. 140-141°; ir ($CHCl_3$) 3453 cm^{-1} (NH), 3110 (=CH), 1700 (C=O), 1640 (C=C); nmr ($CDCl_3$) δ 8.10 (s br, 1, NH). 5.90 (s, 1, =CHBr), 2.40 (q, J = 8 Hz, 2, CH_3-$\underline{CH_2}$), 1.85 (s, 3, ring-CH_3), 1.12 (t, J = 8 Hz, 3, $\underline{CH_3}$-CH_2); uv (95% EtOH) 282 nm (ε 19,000).

2,4-Dimethyl-5-carboxy-1H-pyrrole-3-propanoic Acid (X).- A mixture of ethyl 4-(2-ethoxycarbonylethyl)-3,5-dimethyl-1H-pyrrole-2-carboxylate (IX) (8 g, 0.03 mol),[13] sodium hydroxide (6 g, 0.15 mol), 30 ml water and sufficient ethanol to make a homogeneous solution was stirred and heated on a steam bath for 2 hr. The ethanol was removed in vacuo, the

remaining aqueous solution chilled in an ice-salt bath and neutralized slowly with stirring by dropwise addition of 94 ml of 10% nitric acid. The precipitate was suction-filtered, washed with several portions of cold water and dried in a vacuum desiccator. The slightly pink powder (5.8 g, 92%) was too unstable to be purified. Nmr (pyridine-d_5) δ 13.30 (s br, 2, COOH), 11.40 (s br, 1, NH), 2.53-3.23 (m, 7, CH_2CH_2 and ring-CH_3), 2.67 (s, 3, ring-CH_3).

2,4-Dimethyl-1H-pyrrole-3-propanoic acid (IV).- 2,4-Dimethyl-5-carboxy-1H-pyrrole-3-propanoic acid (X, 1.44 g, 6.8 mmol) was added to 5 ml of nitrogen-saturated water and the mixture heated on the steam bath for 30 min with nitrogen bubbling through it. After cooling to room temperature, the solution was extracted with eight 10 ml portions of ether, the ether removed *in vacuo* and the residue dried in a vacuum desiccator. The light yellow crystalline solid (0.90 g, 79%) had mp. 139-142°, lit.[14] mp. 140-141°, and was used without purification. Nmr (pyridine-d_5) δ 10.13 (br, 2, NH, COOH), 6.45 (unresolved multiplet, 1, ring-H), 2.92 (m, 4, CH_2CH_2), 2.28 (s, 3, ring-CH_3) 2.22 (s, 3, ring-CH_3).

Methyl 5-[(1,5-Dihydro-3-ethyl-4-methyl-5-oxo-2H-pyrrol-2-ylidene) methyl]-2,4-dimethyl-1H-pyrrole-3-propanoate (Ib).[8]- A solution of pure 2-bromomethylene-3-ethyl-4-methyl-3-pyrrolin-5-one (III, 1.23 g, 5.7 mmol) in 25 ml of absolute methanol[16] was added to 2,4-dimethyl-1H-pyrrole-3-propanoic acid (IV, 0.95 g, 5.7 mmol), the mixture refluxed for 1.5 hr under nitrogen, then cooled to -5°. The yellow precipiate was collected by filtration (1.20 g, 67%) and had mp. 216-218°, lit.[8] mp. 213°. A sample (0.937 g) was purified by dissolving it in 300 ml chloroform and extracting with 10 mM sodium hydroxide. The chloroform solution was dried (Na_2SO_4) and concentrated *in vacuo*. The residue was recrys-

tallized from benzene to give 0.728 g of bright yellow needles, mp. 217.5-220.0°. Spectra: ir ($CHCl_3$) 3360 cm^{-1} (N-H), 1728 (ester C=O), 1663 (lactam C=O), 1630 (C=C); nmr ($CDCl_3$) δ 11.23 (s br, 1, NH), 10.30 (s br, 1, NH), 6.10 (s, 1, =CH), 3.67 (s, 3, OCH_3), 2.20-3.00 (m, 9, $C\underline{H}_2CH_3$, $CH_2C\underline{H}_2$, ring-CH_3), 2.13 (s, 3, ring-CH_3), 1.93 (s, 3, ring-CH_3), 1.17 (t, J = 8 Hz, 3, CH_2-$C\underline{H}_3$); uv (95% EtOH) 414 nm (ε 25,800); mass spectrum[17] (164°, 70 eV) m/e 317 ($M^{\cdot+}$ + 1, 18.4%), 316($M^{\cdot+}$, 100%), 244 (11.6%), 243 ($M^{\cdot+}$-($\cdot CH_2COOCH_3$), 64.4%).

5-[(1,5-Dihydro-3-ethyl-4-methyl-5-oxo-2H-pyrrol-2-ylidene) methyl]-2,4-dimethyl-1H-pyrrole-3-propanoic Acid (Xanthobilirubic Acid, Ia).[6]- The methyl ester Ib (1.46 g, 4.62 mmol) was suspended in 150 ml of 10% sodium hydroxide and the mixture (protected from light) stirred and refluxed under nitrogen for 3.5 hr. The reaction mixture was cooled in ice and then filtered to isolate the bright yellow insoluble sodium salt of Ia, which was washed with two 75 ml portions of chloroform to remove unhydrolyzed ester (0.26 g, 18% recovered). The sodium salt was suspended in 75 ml of 10% hydrochloric acid and stirred under nitrogen, protected from light, for 15 min, the mixture filtered and the collected yellow solid washed with cold water and dried in a vacuum desiccator over calcium sulfate. The yield of Ia was 0.905 g (79% based on unrecovered ester). The melting point (lit.[6] mp. 290-291°) was difficult to observe because the material began to decompose at 285°. The material was pure by tlc (Silica gel F, 5% acetic acid/chloroform and polyamide, methanol-10% ammonia-water (9:1:2, v:v:v)). Spectra: ir (Nujol) 3360 cm^{-1} (NH), 3200-2500 (COOH), 1705 (carboxyl C=O), 1670 (lactam C=O), 1630 (C=C); nmr (DMSO-d_6) δ 11.83 (very broad, 1, COOH), 10.18 (s br, 1, NH), 9.67 (s, br, 1, NH), 5.93 (s, 1, =CH), 2.25-2.80 (m, 6, $C\underline{H}_2CH_3$, $C\underline{H}_2C\underline{H}_2$ and residual protons from solvent), 2.22 (s, 3, ring-CH_3), 2.07 (s, 3, ring-CH_3),

1.81 (s, 3, ring-CH_3), 1.10 (t, J = 7 Hz, 3, $CH_2\underline{CH_3}$); uv (MeOH) 416 nm (ε 33,700); mass spectrum[17] (246°, 70eV) m/e 303 ($M^{\cdot+}$ + 1, 18.6%), 302 ($M^{\cdot+}$, 92.9%), 287 ($M^{\cdot+}$ - CH_3, 26.4%), 273 ($M^{\cdot+}$ - $\cdot CH_2CH_3$, 13.6%), 244 (18.6%) 243 ($M^{\cdot+}$ - $\cdot CH_2COOH$, 100%).

REFERENCES

1. Supported in part by National Institutes of Health Grant No. 5R01HD0552.
2. H. Fischer and H. Orth, "Die Chemie des Pyrrols," Vol. I-II, Akademische Verlagsgesellschaft M.B.H., Leipzig, 1934-1940.
3. J. O. Grunewald and E. R. Strope, Abstract No. 410, 9th Midwest Meeting, American Chemical Society, Lawrence, Kansas, October 25-26, 1973.
4. D. A. Lightner, Photochem. Photobiol., 19, 457 (1974).
5. D. Bergsma, D. Y. Hsia and C. Jackson, "Bilirubin Metabolism in the Newborn," Williams and Wilkins, Baltimore, 1970.
6. Ref. 2, Vol II, Part 1, p. 121-126.
7. H. Fischer, T. Yoshioka and P. Hartmann, Zeit. Physiol. Chem., 212, 146 (1932).
8. H. Fischer and P. Hartman, ibid., 226, 116 (1934).
9. Aldrich Chemical Co., Milwaukee, Wis.
10. Ref. 2, Vol. I, pp. 284-287.
11. Use of HCN can be avoided by introducing a formyl group using N,N-dimethylformamide in a modified Vilsmier-Haack procedure; see E. J-H. Chu and T. C. Chu, J. Org. Chem., 19, 266 (1954).
12. J. L. Simonsen, J. Chem. Soc., 93, 1777 (1908).
13. Ref. 2, Vol. I, p. 239.
14. E. Bullock, A. W. Johnson, E. Markham and K. B. Shaw, J. Chem. Soc. 1430 (1958).
15. H. Fischer and C. Nenitzescu, Ann., 443, 113 (1925); F. Morsingh and S. F. MacDonald, J. Am. Chem. Soc., 82, 4377 (1960).
16. A. I. Vogel, "Practical Organic Chemistry," 3rd ed., pp. 169-170, Longmans Group Ltd., London, 1956.

17. A. H. Jackson, G. W. Kenner, H. Budzikiewicz, C. Djerassi and J. M. Wilson, Tetrahedron, 23, 603 (1967). It is obvious that the mass spectrum of compound XXXII in this reference is that of the methyl ester of xanthobilirubic acid (Ib, $M^{+\cdot}$ 316), rather than of the free acid (Ia), as Structure XXXII would indicate.

(Received January 31, 1975; in revised form May 27, 1975)