Synthesis and Properties of Homomologated and Contracted Dipyrrinone Analogs of Xanthobilirubic Acid

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Dipyrrinone analogs of xanthobilirubic acid, 5-[1,5-didehydro-3-ethyl-4-methyl-5-oxo-2*H*-pyrrol-2-ylidene)-methyl]-2,4-dimethyl-1*H*-pyrrol-3-propanoic acid, with alkanoic acid chain lengths varying from formic to caproic have been synthesized as their methyl esters and characterized spectroscopically. All of the dipyrrinones studied exhibit intermolecular hydrogen bonding in chloroform, as detected by ^{1}H-nmr, and the influence of the carboxyl group on the uv-visible spectrum decreases with increasing chain length.

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Introduction.

Dipyrrinones resembling one-half of the important bile pigment, bilirubin, have proved invaluable as model compounds for understanding the complex spectroscopic, photochemical, stereochemical and solution properties of linear tetrapyrrole pigments [1-3] and for use as precursors to synthetic analogs of bilirubin [4,5]. For example, the uv-visible and circular dichroism spectra of bilirubins originate from an exciton coupling between their component dipyrrinones [6], and the regioselective carbon-carbon double bond configurational isomerization of bilirubins [1,7,8] similarly depends on an exciton interaction. In most of the dipyrrinone model compounds studied previously, where a pendant carboxyl or carbomethoxy group was present on the pyrrole ring of the dipyrrinone, it was invariably at the end of a three carbon side chain, consistent with the presence of propionic acid groups in bilirubin. However, the influence of the carboxyl or carbomethoxy group on the properties of dipyrrinones, although of great importance to bilirubins [1,6], has not been examined. In the following we describe the syntheses and properties of analogs of xanthobilirubic acid methyl ester with alkanoic side chains varying from one to six carbons. These dipyrrinones are also important because they may serve as synthetic precursors to symmetric tetrapyrrole analogs of bilirubin with varying lengths of the alkanoic side chains, which are responsible for the stabilization of folded, intramolecularly hydrogen-bonded conformations [1-5].

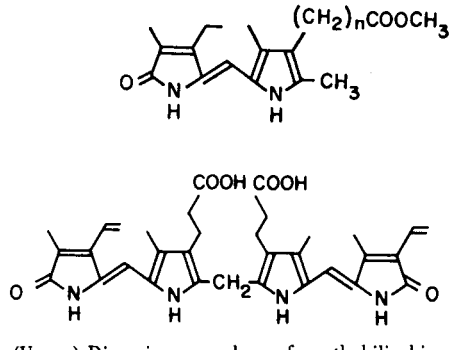


Figure 1. (Upper) Dipyrrinone analogs of xanthobilirubic acid methyl ester (n = 2). (Lower) Linear representation for bilirubin-IXα.

Syntheses.

The syntheses of dipyrrinones (n = 1-5) follow the general outlines of the modified [10] Fischer-Grunewald [9] synthesis of xanthobilirubic acid methyl ester. The final synthetic step involved coupling of 5-bromomethylene-4-ethyl-3-methyl-3-oxo-1*H*-pyrrole with the appropriate 2,4-dimethyl-5-carboxy-1*H*-pyrrole-3-alkanoic acid as outlined in Figure 2. Since the left half is common to all of the dipyrrinones of this work, and the synthesis of corresponding bromomethylene-oxopyrrole reaction component has been described previously [9,11], it will not be discussed here, Rather, we focus on the preparation of the right half pyrrole dicarboxylic acid precursors.

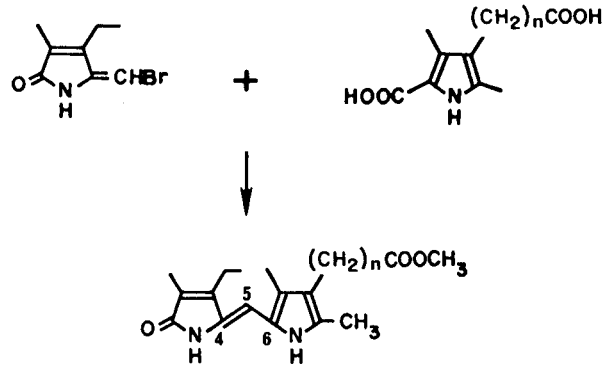


Figure 2. Final step in the synthesis of dipyrrinones. The reaction is carried out in refluxing methanol, in which the dicarboxylic acid component undergoes decarboxylation of the α-COOH.

Alkylation of pentane-2,4-dione at C-3 with the appropriate ω-bromoalkanoic acid (Figure 3) in refluxing dichloromethane or acetonitrile-dimethylsulfoxide with potassium carbonate + cesium carbonate generates the mono *C*-alkylated product in excellent yield. The use of cesium carbonate greatly facilitates the reaction, leading to higher yields of *C*-alkylated product than with potassium carbonate above. The % yield of *C*-alkylated product decreases somewhat with increasing chain length (~95% for n = 1 to ~70% for n = 5), the percent *O*-alkylation increases with increasing chain length (~5% for n = 1 to ~27% n = 5). When potassium carbonate in acetone is used the percent *C*-alkylation drops (~40% for

n = 1 to ~25% for n = 5), and the precent *O*-alkylated product rises to ~50% for n = 5. Curiously, the percent enol present at room temperature in the mono *C*-alkylated product decreases with increasing chain length (from ~33% for n = 1 to 1-2% for n = 5), as determined from ^{1}H-nmr measurements in deuteriochloroform. Mono *C*-3-alkylated pentane-2,4-dione (n = 1-5), either pure or contaiminated with *O*-alkylated by-product was condensed (Figure 3) with ethyl acetoacetate [10] to yield a pyrrole diester (n = 1-5), which could be saponified to give the diacid in high yield. The latter undergoes decarboxylation at the pyrrole α-carbon *in situ* during the condensation step (Figure 2).

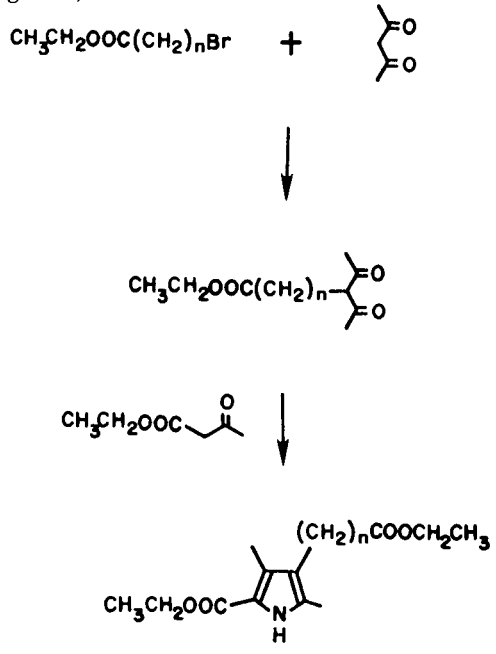


Figure 3. Steps in the synthesis of the dicarboxylic acid pyrrole component of the dipyrrinone synthesis (Figure 1). The diester is converted to the diacid by saponification in ethanolic-aqueous sodium hydroxide.

Synthesis of the n = 0 dipyrrinone ethyl ester was achieved by condensation of the bromomethylene-oxopyrrole (Figure 2) with ethyl 2,4-dimethyl-3-carboxylate. The latter was not prepared as in Figure 3 but rather by selective saponification of the α-carboethoxy group of the diethyl ester of 3,5-dimethyl-2,4-dicarboxylic acid prepared by Fischer-Knorr pyrrole synthesis using only ethyl acetoacetate [12]. It may be noted that the partial saponification product 4-carboxyethyl-3,5-dimethylpyrrole-2-carboxylic acid did not undergo decarboxylation *in situ* during the condensation, but its decarboxylated product, ethyl 2,4-dimethylpyrrole-3-carboxylate underwent smooth coupling with the bromomethylene-oxopyrrole.

Spectral and Chromatographic Properties.

Consistent with previous work [1,3,4,9,10], the new dipyrrinones adopt the stable *syn-Z*-configuration at the exocyclic C-4/C-5 carbon-carbon double bond [13], as determined by nmr nOe measurements [14]. In this configuration, intermolecular hydrogen bonding can be achieved through the coordination of lactam and pyrrole NH groups, as detected previously for dipyrrinones like xanthobilirubic acid methyl ester and its analog with carbomethoxy replaced by hydrogen, kryptopyrromethenone [3,10]. As shown in Table 1, the chemical shift values for the lactam hydrogens are all very nearly the same and are consistent with the presence of an intermolecularly hydrogen-bonded dimer (Figure 4). In d_6-dimethyl sulfoxide, the lactam hydrogens undergo a major shift to ~9.7 ppm and the pyrrole hydrogens only a minor shift to ~10.2 ppm, data consistent with a change from an intermolecularly hydrogen-bonded dimer to a monomeric dipyrrinone with hydrogen bonding predominantly to solvent [3,10]. The presence of the carbomethoxy group (*cf* kryptopyrromethenone) and its distance from the pyrrole moieties has very little effect on the N-*H* chemical shifts. Likewise, there is little effect on the other proton chemical shifts (Table 2), except when n = 0. Here, the carbomethoxy group exerts a deshielding effect on the flanking methyl groups at C-7 and C-9.

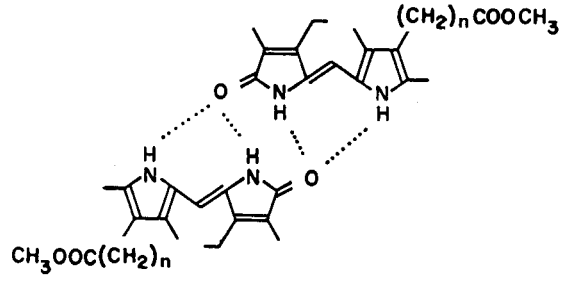
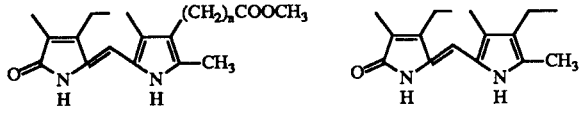


Figure 4. Intermolecularly hydrogen-bonded dipyrrinone dimer.

The location of the carbomethoxy group does, however, exert a detectable influence on the uv-visible spectrum of the dipyrrinones, particularly the intense, long wavelength absorption near 400 nm, which is polarized along the length of the dipyrrinone chromophore [1,15]. The most pronounced effect can be seen (Table 1) for n = 0, where the carbomethoxy group is attached directly to the ring. Since the two flanking pyrrole methyl groups probably destabilize the rotamer which would enable maximum overlap between the carbomethoxy group and the pyrrole ring π-systems (as in 2,6-dimethylacetophenones [16]), the large spectral shift probably originates more, from an inductive effect than a resonance effect. Whatever the origin of the effect, interposition of methylene group between the carbomethoxy and pyrrole groups causes a strong bathochromic shift. Smaller bathochromic shifts attend the interposition of additional methylene units such that only a

Table 1

Summary of Spectroscopic, Chromatographic and Physical Properties of Dipyrrinone Methyl Esters With Varying (n = 0 to 5) Alkanoic Acid Chain Lengths, and Kryptopyrromethenone (KRP)



KRP

n	^{1}H-NMR (ppm) [a] ($CDCl_3$) lactam	pyrrole	UV-Visible (DMSO) [b] λ max	ε	UV Visible ($CHCl_3$) [b] λ max	ε	HPLC Retention Time (min) [c] 20% H_2O	12% H_2O	mp °C
0	11.28	10.65	380	33,200	387	31,800	6.87	4.73	256-257
1	11.20	10.38	404	33,600	402	33,200	4.97	3.97	240 dec
2	11.25	10.35	406	34,400	406	34,000	5.67	4.35	215-217
3	11.35	10.40	411	34,600	407	33,900	7.17	4.42	185-187
4	11.25	10.31	412	35,050	409	32,900	8.21	5.17	177-178
5	11.20	10.27	412	34,450	409	33,600	10.46	5.87	153-155
KRP	11.25	10.30	414	33,800	410	36,150	10.68	6.08	240 dec

[a] For $10^{-3}M$ solutions at 20°, ppm downfield from tetramethylsilane. In d_6-dimethyl sulfoxide the lactam and pyrrole N-*H* chemical shifts are ~9.7 and 10.2 ppm, respectively. [b] For 10^{-5} *M* solutions at 21°. [c] High performance liquid chromatography retention times using at 0.75 ml/min of 0.1 *M* di-*n*-octylamine acetate in methanol (*p*H 7.7) as eluent, containing whit % water specified, and run on a Beckman-Altex Ultrasphere-IP or -ODS column, 5 μm C-18, 25x 0.46 cm with a Beckman-Altex ODS pre-column, 4.5 x 0.46 cm and detecters set at 410 nm.

slight distinction can be drawn between the n = 4 and n = 5 dipyrrinones in their uv-visible spectra. In fact, the spectra of these pigments are very nearly the same as that of kryptopyrromethenone [10], which has no carbomethoxy group. The influence of chain length and solvent on the uv-visible λ max may be seen graphically in Figure 5. As noted previously for xanthobilirubic acid methyl ester (n = 2) and kryptopyrromethenone, the λ max values are smaller in chloroform than in dimethylsulfoxide [10], but whether this is due to hydrogen bonding to solvent (in the latter) or to a solvent-induced conformational effect that changes the rotation angle (ϕ, Figure 5) is as yet unclear.

All of the dipyrrinones of this work have different retention times and separate easily (Table 1) using a slight modification of the powerful reverse phase high performance liquid chromatography (hplc) system developed by McDonagh [17]. The system provides a rough measure of the relative polarity of pigments, with the more polar substances having shorter retention times [17]. In fact, the chromatographic analyses show a continuous lengthening of the retention time of dipyrrinones with increasing length of alkanoic ester side chain. The longest chain (n = 5) ester has retention times approaching those of kryptopyrromethenone, which has no polar carboethoxy group. The presence of a carboethoxy group clearly shortens the retention time, *cf* n = 1 to kryptopyrromethenone - both with the same number of carbons, but as the alkanoic ester chain is lengthened, the dipyrrinone becomes more lipophilic and run as do less polar pigments in the hplc system. The dipyrrinone with n = 0 again does not fit well into the scheme, presumably because the polar part of its carbo-methoxy group is buried between the flanking methyl groups on the pyrrole ring, thus making it less available for interaction with eluent, and the extended nonpolar part (ethyl) imposes a modest lipid character to pigment.

The melting points of the pyrromethenones drop considerably and regularly with lengthening of the alkanoic ester chain. The behavior probably reflects a weakening of crystal forces due to a poorer fit or packing of the long chain pigments into the crystal matrix. Since the crystal structure of a close relative (with ethyl at C-2) of kryptopyrromethenone revealed a packing of intermolecularly hydrogen-bonded dimers with the ethyl groups having their terminal methyls pointed above and below the dipyrrinone plane [13], to accommodate the longer chain methyl ester groups would imply a wider separation of the dimers in the crystal and a weakening of the dimer-to-dimer packing forces, with a resultant lower mp.

In summary, we show that the uv-visible, hplc and mp behavior of a series of new dipyrrinones related to xanthobilirubic acid (Figure 1, n = 0-6) vary in an understandable way and that these pigments exhibit a similar tendency toward the formation of intermolecularly hydrogen-bonded dimers in chloroform. Their conversion to symmetric analogs of bilirubin with varying chain lengths is under study.

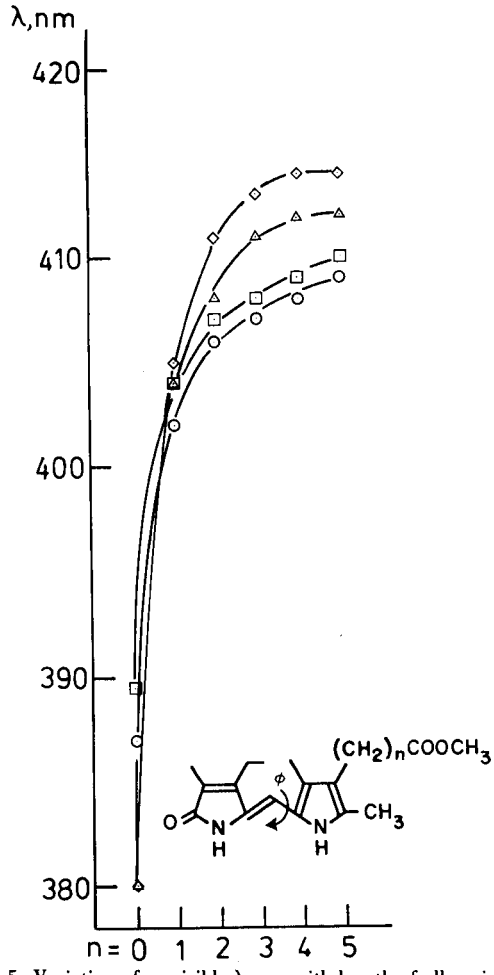


Figure 5. Variation of uv-visible λ max with length of alkanoic ester in dipyrrinones, determined for 10^{-5} *M* solutions in chloroform (○), benzene (□), dimethyl sulfoxide (△) and methanol (◇) at 21°. The rotation angle ϕ has been determined to be ~40° for analogous dipyrrinones in deuteriochloroform (reference [1]).

EXPERIMENTAL

General

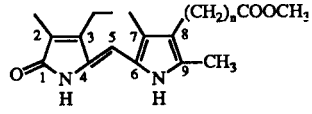
All nmr spectra were run on a GE QE-300 FT spectrometer in either deuteriochloroform (99.9% d_1) or dimethyl sulfoxide-d_6 (99.9% d_6), both from Aldrich. Infrared spectra were run on a Perkin-Elmer 1600 FT-IR spectrophotometer. All uv-visible absorption spectra were run on a Perkin-Elmer model 3840 diode array instrument. Gas chromatography mass spectrometry was accomplished on a Hewlett-Packard GC-MS model 5890A ion selective detector using a DB-1 (100% dimethyl polysiloxane) column. Analytical thin layer chromatography (tlc) was carried out on J.T. Baker silica gel 1B-F plates (125 μ layer). Column chromatography was carried out on 32-63 μ activated silica gel for medium pressure chromatography (M. Woelm). High performance liquid chromatographic (hplc) analyses used a detector set at 410 nm and a Beckman-Altex Ultrasphere-IP 5 μm C-18 ODS column (25 x 0.46 cm), with a Beckman ODS precolumn (4.5 x 0.46 cm) and a flow of 0.75 ml/minute of 0.1 *M* di-*n*-octylamine acetate in 5% aqueous methanol as eluent [17]. Pentane-2,4-dione, ethyl acetoacetate, ω-bromoesters, acetic acid, ethyl acetate, benzene, acetone and hexane were from Aldrich. Spectral grade methanol, chloroform, benzene and dimethyl sulfoxide were from Fisher. Methanol (hplc grade) was from Fisher. All combustion microanalyses were performed by Desert Analytics, Tucson, AZ.

Alkylation of Pentane-2,4-dione.

For alkylation with ethyl bromoacetate, pentane-2,4-dione (150.0 g, 1.5 moles) and ethyl bromoacetate (250.0 g, 1.5 moles) were added to a 2-liter, 3-neck roung bottom flask equipped with condenser and magnetic stirring bar. Dichloromethane (500 ml) was then added, and the solution was stirred at room temperature while anhydrous potassium carbonate (207.3 g, 1.5 moles) and cesium carbonate (2.07 g, 1.0% by weight of potassium carbonate) were added at once. Stirring was continued for 12 hours, at which time analysis by GC-MS indicated the absence of the organic starting materials and the presence of 90% of the

Table 2

Proton Nuclear Magnetic Resonace Data for 10^{-3} *M* Dipyrrinones in Deuteriochloroform at 21 °C



H	n = 0	n = 1	n = 2	n = 3	n = 4	n = 5
CH_3 (2^1)	1.92 (s)	1.89 (s)	1.95 (s)	1.93 (s)	1.95 (s)	1.95 (s)
CH_2 (3^1)	2.54 (q) [a]	2.50 (q) [a]	2.55 (q) [a]	2.53 (q) [a]	2.55 (q) [a]	2.55 (q) [a]
CH_3 (3^2)	1.16 (t) [a]	1.12 (t) [a]	1.17 (t) [a]	1.16 (t) [a]	1.17 (t) [a]	1.17 (t) [a]
=CH (5)	6.14 (s)	6.08 (s)	6.13 (s)	6.15 (s)	6.14 (s)	6.14 (s)
CH_3 (7^1)	2.37 (s)	2.09 (s)	2.14 (s)	2.11 (s)	2.12 (s)	2.12 (s)
CH_2 (8^1)	–	3.36 (s)	2.45 (t) [b]	2.42 (t) [b]	2.40 (t) [b]	2.39 (t) [b]
CH_2 (8^2)	–	–	2.74 (t([b]	1.77 (p) [c]	1.41 (p) [a]	1.31-1.35 (p)
CH_2 (8^3)	–	–	–	2.31 (t) [b]	1.60 (p) [c]	1.60-1.70 (m)
CH_2 (8^4)	–	–	–	–	2.33 (t) [b]	1.31-1.51 (p)
CH_2 (8^5)	–	–	–	–	–	2.31 (t) [b]
CH_3 (9^1)	2.68 (s)	2.37 (s)	2.41 (s)	2.38 (s)	2.39 (s)	2.39 (s)
CH_3 (ester)	[d]	3.62 (s)	3.68 (s)	3.65 (s)	3.66 (s)	3.67 (s)

[a] J = 7.5 Hz. [b] J = 8.0 Hz. [c] quintet, J = 8.0 Hz. [d] Ethyl ester was prepared.

desired mono-*C*-alkylated product, along with 6% *O*-alkylated and 4% dialkylated by-products. Isolation of the desired product was achieved by distillation (90-105° at 0.5 mm Hg).

For alkylations with ethyl 4-bromobutyrate, ethyl 5-bromopentanoate and ethyl 6-bromohexanoate. To a solution containing pentane-2,4-dione (45 g, 0.45 mole) and ω-bromoalkanoic acid ethyl or methyl ester ($Br(CH_2)_nCO_2CH_3$, 0.45 mole) in acetonitrile (3 l) and dimethylsulfoxide (500 ml) was added anhydrous (dried at 150° for 12 hours) potassium carbonate (62 g, 0.5 mole) and cesium carbonate (3 g, 5% by weight of potassium carbonate). The mixture was stirred and heated at 32° for 48 hours. After the first 24 hours, an additional 45 g (0.45 mole) of pentane-2,4-dione was added. The reaction time varied from 16 hours (n = 1) to 50 hours (n = 3) to 5-7 days (n = 4, n = 5). The mixture was cooled, the inorganic salts were removed by filtration, and the filtrate was diluted with chloroform (2 l). The solution was washed with water, (6 x 100 ml) or until no further reduction in volume of the organic layer was observed and the aqueous wash is colorless. The organic layer was dried over anhydrous sodium sulfate, and the chloroform was removed on a rotary evaporator. The last traces of solvent and unreacted pentane-2,4-dione were removed by distillation at 0.5 mm Hg. The desired product was collected by vacuum distillation (0.5 mmg Hg).

Ethyl 3-Acetyl-4-oxopentanoate.

This compound was obtained in 90% yield (33% enol) bp 119-127°, 0.5 mm Hg (lit [18] bp 128-132°, 4.5 mm Hg); ir (film): 3050, 2987, 1731, 1703, 1365, 1196, 1158 cm^{-1}; ^{1}H-nmr: (δ, ppm) (keto) 1.38 (3H, t, J = 7.6 Hz), 2.15 (s, CH_3), 2.68, 2.81 (d, J = 7.2 Hz, 2H), 3.55 (s, OCH_3), 4.30 (t, J = 7.2 Hz) 4.35 (q, J = 7.6 Hz, 2H); (enol) 1.69 (s, CH_3), 1.38 (t, J = 7.2 Hz, 3H), 1.69 (s, 3H), 3.08 (s, CH_2), 3.59 (s, OCH_3) 4.35 (q, J = 7.2 Hz, 2H); ms: m/e (relative intensity) 186 (M^+, 3.5%), 144 (4%), 113 (10%), 98 (20%), 71 (20%), 55 (12%) amu.

Ethyl 5-Acetyl-6-oxoheptanoate.

This compound was obtained in 90% yield (17% enol, 75% mono *C*-alkylation, 25% *O*-alkylation), bp 138-140° (1 mm Hg); ir (film): 2980, 1740, 1705, 1685, 1590 cm^{-1}; ^{1}H-nmr: (δ, ppm) 1.26 (t, J = 7.5 Hz CH_3), 1.50-2.10 (m, 6H), 2.20 (s, CH_3), 2.15 (s, CH_3 of enol), 3.85 (t, J = 7 Hz, 1H), 4.15 (q, J = 7.5 Hz, CH_2 of keto + enol), 16.75 (s, enol OH).

Ethyl 6-Acetyl-7-oxo-octanoate.

This compound was obtained in 74% yield (5% enol, 75% mono *C*-alkylation, 25% *O*-alkylation), bp 124-130° (3 mm Hg); ir (film): 2948, 2863, 1736, 1700, 1583, 1168 cm^{-1}; ^{1}H-nmr: (δ, ppm) 1.2 (t, J = 7 Hz, CH_3), 2.13 (s, CH_3), 2.25 (m, CH_2), 1.5-1.9 (m, 6H), 3.58 (t, J = 7.5 Hz, CH), 3.74 (q, J = 7 Hz, -OCH_2), 4.1 (q, J = 7 Hz, OCH_2) 5.4 (s, =CH of *O*-alkyl), 16.3 (s, OH of enol).

Ethyl 7-Acetyl-8-oxononanoate.

This compound was obtained in 100% yield (1-2% enol, 75% mono *C*-alkylation, 27% *O*-alkylation), bp 130-135° (1 mm Hg), ir (film): 2948, 2863, 1736, 1700, 1679, 1055, 1583, 1168 cm^{-1}; ^{1}H-nmr: (δ, ppm) 1.23 (t, J = 7 Hz, CH_3), 1.25-1.85 (m, 8H), 2.14, 2.12, 2.10 (s, CH_3CO), 2.28 (m, -CH_2CO), 3.58 (t, J = 7.5 Hz, 1H), 3.75 (t, J = 8 Hz, OCH_2-), 4.10 (q, J = 7 Hz, -OCH_2CH_3), 5.42 (s, =CH), 16.1 (s, OH enol).

Fischer-Knorr Pyrrole Synthesis.

To a solution of ethyl acetoacetate (104 g, 0.80 mole) dissolved in glacial acetic acid (300 ml) was added (dropwise) a solution of sodium nitrite (61.5 g, 0.89 moles) in 150 ml of water with efficient stirring while keeping the solution below 14° (ice bath). The solution was then allowed to warm to room temperature overnight. With efficient mechanical stirring, the appropriate acetyl-oxo-alkanoate ester (above (0.80 mole) was added in one batch, followed by 120 g (1.84 g-atoms) of zinc in small portions so as to keep the temperature below 65° during the addition. After the zinc has completely dissolved, the reaction mixture was stirred for 4 hours then heated overnight at 95° with stirring. The hot reaction mixture was the poured into 4 liters of water + ice. The resulting precipitate of crude pyrrole was collected by filtration.

3,5-Dimethyl-2-(ethoxycarbonyl)-1*H*-pyrrole-3-ethanoic Acid Methyl Ester.

This compound was recrystallized from ethanol to give a 50% yield of pure product, mp 120-122°; ir (potassium bromide): 3280, 2900, 1730, 1650, 1435, 1260, 1150, 1090, 1015, 990 cm^{-1}; ^{1}H-nmr: (δ, ppm) 1.35 (t, J = 7 Hz, CH_3), 2.30 (s, 2 x CH_3), 3.45 (s, -CH_2-C=O), 3.68 (s, OCH_3), 4.35 (q, J = 7 Hz, O-CH_2-), 9.30 (brs, NH)).

Anal. Calcd. for $C_{12}H_{17}NO_4$ (239.3): C, 60.24, H, 7.16; N, 5.85. Found: C, 60.03; H, 7.15; N, 5.84.

3,5-Dimethyl-2-(methoxycarbonyl)-1*H*-pyrrole-3-butanoic Acid Ethyl Ester.

This compound was recrystallized from ethanol-hexane 1:1 to give an 48% yield of pure product, mp 74-75°; ir (potassium bromide): 3400, 3320, 2980, 2965, 2860, 1730, 1685, 1670, 1500, 1455, 1420, 1375, 1170, 1220, 1100, 700 cm^{-1}; ^{1}H-nmr: (δ, ppm) 1.30 (t, J = 7 Hz, CH_3), 2.23 (s, CH_3), 2.30 (s, CH_3), 1.60-2.80 (m, 6H), 3.85 (s, OCH_3), 4.15 (q, J = 7 Hz, O-CH_2-), 9.12 (brs, NH).

Anal. Calcd. for $C_{14}H_{21}NO_4$ (267.3): C, 62.90; H, 7.92; N, 5.24. Found: C, 63.18; H, 8.16; N, 5.07.

3,5-Dimethyl-2-(ethoxycarbonyl)-1*H*-pyrrole-3-pentanoic Acid Ethyl Ester.

This compound was recrystallized from ethanol to afford 45% of the pure pyrrole, mp 79-81°; ir (film): 3314, 2976, 2932, 2856, 1735, 1662, 1440, 1377, 1271, 1174, 1098 cm^{-1}; ^{1}H-nmr: (δ, ppm) 1.20 (t, J = 7 Hz, CH_3), 1.30 (t, J = 7 Hz, CH_3), 1.40, 1.60 (2x quintets, -CH_2-CH_2-CH_2-CH_2-CH_2-), 2.34 (t, -CH_2-CO), 4.08 (q, J = 7 Hz, O-CH_2), 4.24 (q, J = 7 Hz, O-CH_2), 8.50 (brs, NH).

Anal. Calcd. for $C_{16}H_{25}NO_4$ (295.4): C, 65.06; H, 8.53; N, 4.76. Found: C, 65.09; H, 8.48; N, 4.65.

3,5-Dimethyl-2-(ethoxycarbonyl)-1*H*-pyrrole-3-hexanoic Acid Ethyl Ester.

This compound was recrystallized from ethanol to afford 33% of the pure pyrrole, mp 61-63°; ir (film): 3314, 2981, 2932, 2858, 1738, 1661, 1504, 1442, 1377, 1271, 1218, 1174, 1100, 1026 cm^{-1}; ^{1}H-nmr: (δ, ppm) 1.24 (t, J = 7 Hz, CH_3), 1.34 (t, J = 7 Hz, CH_3), 1.31, 1.40 1.60 (3x quintet, 6H of -CH_2-CH_2-CH_2-CH_2-CH_2-), 2.18 (s, CH_3), 2.25 (s, CH_3), 2.28 (t, J = 7 Hz, CH_2-CO), 2.34 (t, J = 7 Hz, pyrrole -CH_2-), 4.15 (q, J = 7 Hz, O-CH_2-), 4.29 (q, J = 7 Hz, O-CH_2), 8.50 (m, NH).

Anal. Calcd. for $C_{17}H_{27}NO_4$ (309.4): C, 65.99; H, 8.80; N, 4.52. Found: C, 65.89; H, 8.76; N, 4.42.

3,5-Dimethyl-2-carboxy-1*H*-pyrrole-3-alkanoic Acid (n = 1-5).

The diester (20 mmoles) was dissolved in 30 ml of ethanol and treated with a solution of 4.0 g (100 mmoles) of sodium hydroxide

in 15 ml of water containing 5 g/10 ml of sodium nitrite. The mixture was heated at reflux for 2 hours. The ethanol was removed using a rotary evaporator; then, the remaining solution was cooled to -10 to -15° while a solution of 10 ml of concentrated nitric acid in 60 ml of water containing 5 g/10 ml of sodium nitrite was added. The temperature of the mixture remains below -8° and the sodium nitrite prevents freezing. The diacid precipitated as a white solid and was collected by filtration and washed three times with 20 ml of ice water. After suction filtration for 15 minutes, the white solid diacid was transferred to a Petri dish, dried in a vacuum desiccator and used directly in the coupling reaction. The yields of the pyrrole diacids were: ethanoic acid (95%), butanoic acid (85%), pentanoic acid (75%) and hexanoic acid (84%).

Ethyl 2,4-Dimethylpyrrole-3-carboxylate.

3,5-Dimethylpyrrole-2,4-dicarboxylic and dimethyl ester (10 g, 42 mmoles), prepared [12] by Fischer-Knorr condensation of ethyl acetoacetate, was dissolved in 80 ml of ethanol and treated with a solution of 5 g of potassium hydroxide in 100 ml of water. The solution was heated at reflux under nitrogen with stirring (approximately 2 hours) until an aliquot showed no precipitation when dropped into water. The hot solution was filtered, cooled and washed with ether. The aqueous layer was acidified with acetic acid, and 3,5-dimethyl-4-carboethoxypyrrole-2-carboxylic acid precipitated. Recrystallization from ethanol gave 3.5 g (40%) of beige crystals with mp 217-221° dec with carbon dioxide evolution. This material (6.3 g, 30 mmoles) was heated slowly under nitrogen and with stirring until no more carbon dioxide was evolved. The resulting dark red oil was then distilled at 106° (13 mm Hg) to afford a clear liquid, which solidified upon cooling. Recrystallization from hexane-ethyl acetate (25:1) gave colorless crystals, 4.05 g (80% yield) and mp 75-76° (lit [12] mp 75-76°); ^{1}H-nmr: δ ppm 1.32 (t, 3H, J = 7 Hz), 2.22 (s, 3H), 2.15 (s, 3H), 4.22 (q, 2H, J = 7 Hz), 6.20 (s, 1H), 8.15 (brs, 1H, NH).

5-[1,5-Didehydro-3-ethyl-4-methyl-5-oxo-2*H*-pyrrol-2-ylidene)-methyl]-2,4-dimethyl-1*H*-pyrrol-3-alkanoic Acid Methyl Ester (n = 1-5).

5-Bromomethylene-4-ethyl-3-methyl-2-oxo-1*H*-pyrrole (20 mmoles) [9-11] and 20 mmoles of a diacid (above) were dissolved in 150 ml of methanol + 1 ml of water and heated at reflux under nitrogen with stirring for 12 hours. The mixture was cooled to room temperature then placed in the freezer for 24 hours. The resultant yellow precipitate was collected by filtration and washed with cold methanol and recrystallized from oxygen-degassed benzene. Additional product could be obtained from the mother liquors by crystallizing from oxygen degassed benzene-hexane. The dipyrrinones thus obtained had alkanoic acid methyl ester side chains -$(CH_2)_nCO_2CH_3$(Figure 1) with the following yields and properties.

Methyl Ester, n = 1.

This compound was obtained, 72% yield; ir (potassium bromide) 3450, 3360, 2980, 2940, 2885, 1740, 1670, 1635, 1460, 1440, 1270, 1175, 1100, 690 cm^{-1}; uv-visible: λ max 405 nm, ϵ, 36,100 λ max 265 sh nm, ϵ, 4000, λ max 233.5 nm, ϵ, 8000 (methanol), additional uv-visible data, mp and ^{1}H-nmr in Tables 1 and 2.

Anal Calcd. for $C_{17}H_{22}N_2O_3$ (302.4): C, 67.53; H, 7.33; N, 9.26. Found: C, 67.25; H, 7.36; N, 9.20.

Xanthobilirubic Acid Methyl Ester n = 2.

This compound was obtained 71% yield [10] with relevant data in Tables 1 and 2; uv-visible: λ max 411 nm, ϵ, 37,700 (methanol).

Methyl Ester, n = 3.

This compound was obtained in a yield of 70%; ir (neat): 3350, 3194, 2965, 2932, 2867, 1730, 1682, 1635, 1440, 1374, 1174 cm^{-1}; uv-visible: λ max 413, ϵ, 37,300, λ max, 267.5, ϵ, 4,700, λ max 235.5, ϵ, 10,000 (methanol); ^{1}H-nmr in Tables 1 and 2.

Anal. Calcd. for $C_{19}H_{26}N_2O_3$ (330.4): C, 69.06; H, 7.93; N, 8.48. Found: C, 69.20; H, 8.09; N, 8.38.

Methyl Ester, n = 4.

This compound was obtained in a yield of (77%); ir (neat): 3354, 3183, 3150, 2965, 2936, 2856, 1741, 1668, 1623, 1601, 1583, 1463, 1371, 1266, 1172, 676 cm^{-1}; uv-visible: λ max 414, ϵ, 37,200, λ max 281, ϵ, 4900, λ max 233, ϵ, 9500 (methanol); ^{1}H-nmr in Tables 1 and 2.

Anal. Calcd. for $C_{20}H_{28}N_2O_3$ (344.5): C, 69.74; H, 8.19; N, 8.13. Found: C, 69.77; H, 8.15; N, 7.87.

Methyl Ester, n = 5.

This compound was obtained in a yield of 70%; ir (film): 3361, 2920, 2850, 1736, 1679, 1633, 1605, 1583, 1464, 1436, 1374, 1267, 1171 cm^{-1}; uv-visible: λ max 414, ϵ, 38,900, λ max 281, ϵ, 4900, λ max 232.5, ϵ, 10,200 (methanol); ^{1}H-nmr in Tables 1 and 2.

Anal. Calcd. for $C_{21}H_{30}N_2O_3$ (358.5): C, 70.36; H, 8.43; N, 7.82. Found: C, 70.45; H, 8.42; N, 7.65.

5-[1,5-Didehydro-3-ethyl-4-methyl-5-oxo-2*H*-pyrrol-2-ylidene)-methyl]-2,4-dimethyl-1*H*-pyrrol-3-carboxylic Acid Ethyl Ester (n = 0).

5-Bromomethylene-4-ethyl-3-methyl-3-2-oxo-1*H*-pyrrole (650 mg, 3 mmoles) was heated at reflux in 75 ml of ethanol under nitrogen with stirring for 24 hours to 3 days. The reaction was cooled and the ethanol was removed on a rotary evaporator. The residue was chromatographed on silica gel using dichloromethane-methanol (50:1) as eluent to afford a yellow-orange solid, which was recrystallize from benzene or benzene-hexane (1:1) to give 180 mg (20%) of desired dipyrrinone.

Ethyl Ester, n = 0.

This compound was obtained in a yield of 20%; ir (neat): 3337, 2965, 1698, 1681, 1634, 1578, 1285, 1257, 1120, 1100 cm^{-1}; uv-visible: λ max 380, ϵ, 33,400, λ max 248 (sh), ϵ 11,800, λ max 219.3, ϵ, 16,100 (methanol); ^{1}H-nmr in Tables 1 and 2.

Anal. Calcd. for $C_{17}H_{22}N_2O_3$(302.4): C, 67.53; H, 7.33; N, 9.26. Found: C, 67.85; H, 7.31; N, 9.28.

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