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Polymer Bound Pyrrole Compounds, VII [1]: Xanthobilirubinic Acid Esters and Amides from an Insoluble, Polystyrene-Supported Precursor [2]

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Summary. A series of xanthobilirubinic acid (*XBR*) esters (i.e., **1c** to **1p**) and amides (**2a–2c**) have been prepared by a procedure involving detachment of the chromophore previously ester-bound to a functionalized, insoluble polystyrene (**1b**). Detachment is achieved by treatment with the respective alcohol in aqueous alkali or with the amines, yielding directly the corresponding esters or amides. With primary, short-chained alcohols the ester yields are high (60% for n-C_4H_9-OH to 99% for C_2H_5-OH), but decrease rapidly with chain length (40% for n-$C_{10}H_{21}$-OH and 0% for n-$C_{16}H_{33}$-OH). The same trends are observed with the amines. These results are interpreted in terms of an (increasingly) unfavourable entropic interaction between the polymer matrix to which the chromophore is bound and the (growing) alcohol chain. The impairment by the long chained nucleophile to reach the transesterification center could also contribute, and, for the most lipophylic alcohols, their low solubility in aqueous alkali is an additional drawback. With secondary and tertiary alcohols, no ester is obtained, in agreement with a $B_{AC}2$ mechanism involving a tetrahedral intermediate.

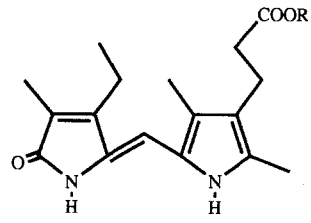
Keywords. Xanthobilirubinic acid esters and amides; Alcoholysis; Aminolysis; Polystyrene bound precursor.

Polymergebundene Pyrrolverbindungen, 7. Mitt. [1]: Darstellung von Xanthobilirubinsäureestern und -amiden, ausgehend von einer unlöslichen polystyrolgebundenen Vorstufe [2]

Zusammenfassung. Unlösliche, durch eine Estergruppe an Polystyrol gebundene Xanthobilirubinsäurederivate liefern mit Alkoholen die monomeren Ester (**1c–1p**), mit Aminen die monomeren Amide (**2a–2c**). Die Ausbeuten für primäre kurzkettige Alkohole sind hoch (n-C_4H_9-OH: 60%, C_2H_5-OH: 99%), mit steigender Kettenlänge sinken sie rasch (n-$C_{10}H_{21}$-OH: 40%, n-$C_{16}H_{33}$-OH: 0%). Denselben Trend beobachtet man bei Aminen. Die Ergebnisse werden durch eine zunehmend ungünstige entropische Wechselwirkung zwischen Chromophor an der Matrix und Alkohol interpretiert. Durch die steigende Kettenlänge des Alkohols könnte auch aus räumlichen Gründen die Annäherung des Nucleophils an das Reaktionszentrum erschwert werden. Die geringe Löslichkeit der höheren lipophilen Alkohole in wäßrigem Alkali wirkt sich ebenfalls ungünstig auf den Reaktionsverlauf aus. Für sek. und tert. Alkohole wird keine Reaktion erhalten, wie es für einen $B_{AC}2$-Mechanismus mit tetraedrischem Zwischenprodukt zu erwarten ist.

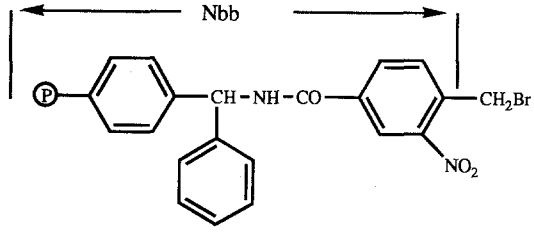
Introduction

We have recently reported [3] an efficient procedure for the covalent binding of di- and tetrapyrroles to an insoluble, microporous polymer, the so-called bromo-



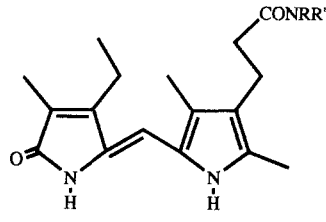
1

1	-R
a	-H
b	$-CH_2$Nbb
c	$-CH_3$
d	$-CH_2CH_3$
e	$-(CH_2)_2CH_3$
f	$-(CH_2)_3CH_3$
g	$-(CH_2)_9CH_3$
h	$-(CH_2)_{15}CH_3$
i	$-CH_2$Ph
j	$-CH_2CH(CH_3)_2$
k	$-CH_2C(CH_3)_3$
l	$-CH(CH_3)_2$
m	$-CH(CH_3)CH_2CH_3$
n	$-C(CH_3)_3$
o	$-CH_2CH_2OH$
p	$-CH_2CH_2$OXBR



3

Ⓟ stands for poly(styrene-co-1%-divinylbenzene)



2

2	-R	-R'
a	-H	$-CH_3$
b	$-CH_3$	$-CH_3$
c	-H	$-CH(CH_3)$Ph

methyl-Nbb resin (**3**); i.e., α-[(4-bromomethyl-3-nitrobenzamido)benzyl]-poly-(styrene-co-1%-divinylbenzene). The dipyrrinone *XBR* (**1a**) could thus be linked to the macromolecule as an ortho-nitrobenzyl ester (**1b**), and this converted its carboxylic acid group into an activated form. Subsequently, *XBR* could be quantitatively detached from the polymer by a base catalyzed transesterification which gave the methyl ester derivative **1c**.

The aims of the present work were to check: (1) the generality of this alcoholysis reaction as well as the factors (steric, electronic, polarity, etc.) influencing it; and (2) whether the process could be extended to other nucleophilic groups such as amines, to give the corresponding *XBR* amides **2**.

Even though many procedures are available for the synthesis of esters and amides, only a few have been utilized for di- and tetrapyrroles (e.g. [4, 5]): dicyclohexylcarbodiimide/dimethylamino-

pyridine, (*DCCI/DMAP*) has been successfully used in the preparation of *XBR* esters of secondary alcohols [4b], but the procedure yields difficultly separable mixtures of products for bilirubin (*BR*). On the other hand, nucleophilic substitution of several alkyl halides, tosylates and mesylates by *XBR* carboxylate is also a good procedure [6a], but when applied to bilirubin only the corresponding monoesters are obtained [6b]. Finally, the use of Shioiri's reagents diphenylphosphoryl azide (*DPPA*) [5a] and diethylphosphorocyanidate (*DEPC*) [5b] seems adequate for the synthesis of *XBR*- [5c, 5d] and *BR*-amides [5e], but not for the corresponding esters. In any case, the development of an additional procedure for the preparation of esters and amides of pyrrole pigments seems desirable, and in this respect the present results should also be considered as preliminary to others where the synthetic procedures developed here should be applied to *BR* and biliverdin (*BV*).

Results and Discussion

Detachment with Alcohols

Room temperature treatment of polystyrene-bound *XBR*, **1b** (ca. 0.85 meq of chromophore per g of solid) with dioxane: alcohol: 4*N* aqueous base (NaOH or KOH) mixtures (30 : 9 : 1) (concentration of base in the mixture is 0.1 *N*) under the conditions given in the experimental part, yields the respective *XBR* esters with varying yields (Table 1). With primary, short-chained, linear or branched alcohols, the ester yields are acceptable to excellent, but they decrease rapidly with chain length (no ester is obtained with cetyl alcohol). One apparent reason for these results is the lack of amphiphylicity of the long-chain alcohols; i.e., the impossibility

Table 1. Detachment of *XBR* by dioxane: alcohol (*R*-OH): 4*N*-aqueous base mixtures[a]

R	*XBR* Ester obtained, **1**	Number of washings	Duration of washings (min)	Ester yield (%)	Total *XBR* detached (%)
CH_3	**c**	3	3	95	99
CH_2CH_3	**d**	4	3	95	99
$(CH_2)_2CH_3$	**e**	9	3	88[b]	95
$(CH_2)_3CH_3$	**f**	9	3	51[b]	60
$(CH_2)_9CH_3$	**g**	10	10	39[b, c]	43
$(CH_2)_{15}CH_3$	**h**	1	360	–	20
CH_2Ph	**i**	10	10	25[b]	34
$CH_2CH(CH_3)_2$	**j**	5 × 5 + 4 × 30		69	71
$CH_2C(CH_3)_3$	**k**	10	10	38	76
$CH(CH_3)_2$	**l**	2 × 10 + 8 × 20		4	35
$CH(CH_3)CH_2CH_3$	**m**	8	15	–[b]	20
$C(CH_3)_3$	**n**	10	10	–	30
CH_2CH_2OH[d]	**o, p**	6	5	–	87[e]

[a] Treatment involves repeatedly washing the polystyrene-bound *XBR* (**1b**) with 30 : 9 : 1 dioxane: ROH: 4*N*-aqueous NaOH (KOH when specified)

[b] KOH

[c] When *DMF* was used instead of dioxane, 62% yield of ester was obtained (91% of initial *XBR* detached)

[d] Dioxane: $HOCH_2CH_2OH$: 4*N*-aqueous NaOH 34.5 : 4.5 : 1 was used as detaching mixture

[e] The product is a mixture of **1o** (75%) and **1p** (25%)

to obtain homogeneous solutions. In this respect, the use of KOH in place of NaOH for alcohols of intermediate lengths (see Table 1) improved the yields, as these were increased when sufficient dimethylformamide (*DMF*) was added instead of dioxane so that a deanchoring homogeneous solution was obtained (see Table 1). However, for alcohols of more than 10 carbon atoms, none of the modifications assayed helped. These included the use of other aqueous bases such as tetra-*n*-butyl ammonium hydroxide, tertiary amines such as triethylamine, ethyldiisopropylamine, pyridine and imidazole, as well as non-aqueous dioxane : alcohol : alcoxide mixtures. The insolubility argument however, cannot be the only one accounting for the decreasing yields with chain length: indeed, when a long-chained amphiphylic alcohol [monomethoxypolyethyleneglycol, *MPEG*, of FW = 1900; ca. 43 (CH_2CH_2O)-units] was used, the dioxane : *MPEG* : 4*N*-aqueous NaOH (30 : 9 : 1) mixture was homogeneous, but no *XBR* ester was obtained by this procedure even after prolonged treatment. This might be the result of an unconventional steric effect exerted by the polymer matrix to which the chromophore is bound. Accordingly, the polymer interacts with the alkyl (or polyethyleneglycol) chain of the alcohol, diminishing its mobility and therefore the system entropy. Yet, an additional less important contribution is based on the impairment by the long-chain nucleophile to reach the reactive center of the transesterification process.

With secondary and tertiary alcohols, no ester was obtained, which can be rationalized in terms of a $B_{AC}2$ mechanism [7] for the transesterification step. According to this mechanism, the reaction involves a tetrahedral intermediate and therefore must be more hindered for secondary and tertiary alcohols.

From a preparative point of view, the composition of the detached mixture, containing the target ester plus – in those cases where longer base treatment times are required – some *XBR* free acid, could easily be established by reversed-phase HPLC: under the conditions used, *XBR* showed the shortest retention time (ca. 3 min), while those of the esters were always longer (above 4 min), and increased with alcohol chain length.

All esters prepared have ^{1}H-NMR, IR and UV-VIS spectra similar to the previously reported *XBR* methyl ester **1c**. The ^{1}H-NMR spectra in $CDCl_3$ show the two NH broad singlets near 11.2 and 10.6 ppm characteristic of dipyrrinone dimers [8]. In the IR the appearance of the ester C=O band near 1740 cm^{-1} is accompanied by the disappearance of the acid O-H band (3300 – 2500 cm^{-1}). The UV-VIS absorption maxima in CH_2Cl_2 (410 nm) and *Me*OH (400 nm) also resemble those of **1c**, suggesting that, at least under these conditions, the lateral chain has no effect on the chromophore conformation.

Detachment with Ethyleneglycol

This process is interesting both synthetically and mechanistically. From the synthetic point of view, because it is important to dispose of a simple procedure for the preparation of bichromophoric systems where the chromophore-chromophore distance could be varied by increasing the length of the diol molecule. These systems should be well suited for the study of interchromophoric interactions, especially the exciton coupling and its dependence on geometric parameters. From a mechanistic point of view, the interest comes from the possibility to further investigate the so-called "local concentration effect"; i.e., the higher local concentration of chromophore in the polymer bead (ca. 1 *N* in the present case) as compared to

"standard" concentrations in solution (0.01 to 0.1 *N*). As a result of this higher local concentration of the chromophore, once one -OH end of a given ethyleneglycol molecule has been utilized to detach one *XBR* molecule from the polymer, it should be easier for the second -OH end of the same molecule to find another polymer-bound dipyrrinone unit in its surroundings for transesterification. Consequently, one should expect higher yields of diester **1p** relative to monoester **1o** under solid-state conditions than in a parallel transesterification experiment in homogeneous solution.

Under the conditions given in the experimental part, nearly 90% of polymer-bound *XBR* (**1b**) is detached after 6 (5 min) washings. The product is a ca. 3 : 1 mixture of monoester **1o** and diester **1p**, which corresponds to 60% of polymer-bound *XBR* detached as monoester and 40% as diester. The important percentage of monoester can be explained in terms of the much larger concentration of $^{-}OCH_2CH_2O^{-}$ vs. $^{-}OCH_2O$-*XBR* surrounding the polystyrene-bound *XBR*, **1b** during the detachment procedure. Nucleophilic substitution by the dialcoxide will lead – at least in a first stage – to monoester **1o**, while attack by $^{-}OCH_2CH_2O$-*XBR* should afford the diester **1p**. Additionally, partial saponification of **1p** in aqueous alkali must also contribute to the formation of monoester **1o**.

The spectroscopic properties of ester **1o** and **1p** are also analogous to those of the previously discussed esters. In $CDCl_3$, the ^{1}H-NMR spectra suggest for both compounds dimeric dispositions (probably intramolecular in **1p**). The (intermolecular) hydrogen bonding in **1o** and the (intramolecular?) one in **1p** are equally effective, as proved in two parallel NMR experiments where the chemical shifts of the lactam and pyrrole NH signals of ca. 10^{-3} *M* $CDCl_3$ solutions of **1o** and **1p** were recorded as a function of increasing amounts of *DMSO-d*$_6$ (a hydrogen bond breaking solvent) added to the NMR tubes; for additional details, see Ref. [8]. Similar effects in these chemical shifts were observed in the two cases when the same amount of *DMSO-d*$_6$ was added to each tube.

In the UV-VIS spectra, ε values for **1p** roughly double those of **1o**, as expected. Furthermore, even though the absorption bands both in CH_2Cl_2 and *Me*OH for the two compounds are centered on the same wavelength values, dichromophoric **1p** shows broader bands compared to monochromophoric **1o** (especially in *Me*OH) in agreement with some degree of exciton coupling in the first [9].

Detachment with Amines

An analogous treatment of polymeric *XBR*-O-CH_2-*Nbb* (**1b**) with 4 *N* solutions of several amines in dioxane (see Experimental Part), gave the corresponding amides with good yields (75% for **2a** and 65% for **2b**) for primary, unhindered amines, but poorer results (25% for **2c**) as the steric hindrance of the amine increased. This is in agreement with the $B_{AC}2$ mechanism discussed above for transesterification, and suggests that the same factors operate here.

As with the esters, the composition of the detached mixtures was checked by reversed-phase HPLC, where *XBR* (**1a**) has the lowest retention time. The spectroscopic properties of these *XBR* amides are also analogous to those of the respective esters. In the ^{1}H-NMR two broad singlets near 11 and 10 ppm are consistent with structures basically dimeric, although the smaller chemical shifts, relative to the esters, suggest lower association constants in the amides.

In conclusion, the present method is a useful procedure for the facile preparation of an up-to-100 mg scale (although larger amounts could exceptionally be obtained) of a variety of *XBR* esters (and amides) of primary, short-chain alcohols (and

amines). Since steric factors seem to play an important role in these processes, some of the problems encountered might be overcome by the use of an analogous, macroporous material.

Experimental Part

Dioxane was distilled, sodium was then wired onto it, dioxane decanted and distilled from CaH_2 first and then from $LiAlH_4$. The glycine/HCl buffer was prepared by addition of solid glycine to a 0.04 *M* aqueous HCl solution previously saturated with $(NH_4)_2SO_4$ until a *pH* of 2.5 was reached. 4 *N* Dioxane solutions of methyl and dimethylamine were prepared by refluxing, for a period of 2 h, commercial 40% aqueous solutions of each amine (200 ml), drying the wet gaseous amines with KOH and collecting them onto dioxane (100 ml) kept at 20°C. The normality of each solution was titrated with an excess HCl followed by back titration with NaOH. The resulting solution was eventually adjusted to the desired concentration by dilution. The preparation and properties of *XBR* (**1a**) [5c], the esters *XBR*-O-CH_2*Nbb* (**1b**) [3], *XBR*-O-CH_3 (**1c**) [5c, 10] and *XBR*-O-$CH(CH_3)CH_2CH_3$ (**1m**) [4b] and amides *XBR*-N-CH_3 (**2a**) [5c], *XBR*-$N(CH_3)_2$ (**2b**) [5c], and *XBR*-N-$CH(CH_3)$-*Ph* (**2c**) [5d] are described in the literature.

Melting points were determined on a Kofler-Reichert micro hot-stage apparatus. UV-VIS spectra were recorded on a Perkin-Elmer Lambda 5 instrument. ^{1}H-NMR spectra were determined on a Varian XL-200 (200.6 MHz) instrument. IR spectra were determined on a Perkin-Elmer 681. Mass spectra were recorded an a Hewlett-Packard 5988-A instrument equipped for FAB analysis with a Capillaritron Frasor. Analytical HPLC was carried out on a Waters Radial Pak C18 column (0.8 × 10 cm; particle size: 10 μm) with a Waters double pump (1 ml/min) using a variable wavelength detector 5 FA 339 (detection at 400 nm); $CH_3CN : H_2O$ (100 : 20) solvent system.

General Procedure for the Preparation of Esters **1c–1p**

In a 10 ml polypropylene syringe equipped with a perfectly fitted polyethylene disk in its lower extreme, polystyrene-bound *XBR* (**1b**) (approximate functionality in *XBR* of 0.85 meq. g^{-1} resin; 35 mg; ca. 0.03 meq *XBR*, ca. 9 mg of *XBR* ester expected) was washed (3 × 3 ml × 3 min; for other conditions see Table 1) at room temperature, in the dark and under vigorous Vortex mixing, with an argon saturated, freshly prepared mixture of dioxane : alcohol : 4 *N*-aqueous NaOH (30 : 9 : 1) and the solvent after each washing filtered onto a mixture of $CHCl_3$ (9 ml) and aqueous glycine/HCl buffer (see above; 4–5 ml; starting *pH* = 2.7, final *pH* = 5–6). The first washings were deep yellow, but the colour intensity decreased in subsequent washings. The solvent mixture was taken into a separatory funnel, and the aqueous phase washed with $CHCl_3$ (4 × 10 ml). The $CHCl_3$ layer was washed repeatedly with H_2O to remove any dioxane present, filtered through paper and evaporated. This yielded the respective esters, eventually impure by some *XBR* free acid. The last could be removed by aqueous base extraction.

Xanthobilirubinic Acid Ethyl Ester (**1d**)

Prepared according to the general procedure with a 95% yield. M.p. = 190 °C. HPLC (C18): R_t = 6.2 min (under these conditions, *XBR* (**1a**) has R_t = 3.1 min, and its methyl ester, **1c**, R_t = 4.7 min).

^{1}H-NMR ($CDCl_3$, δ, ppm): 11.19 (s, 1 H, lactam NH), 10.27 (s, 1 H, pyrrole NH), 6.12 (s, 1 H, = CH-), 4.12 (q, *J* = 7.2 Hz, 2 H, -CO_2CH_2-), 2.8–2.2 (m, 6 H, -CH_2CH_2-, -CH_2CH_3), 2.40 (s, 3 H, -$CH_3^{3' \text{ or } 5'}$), 2.12 (s, 3 H, -$CH_3^{5' \text{ or } 3'}$), 1.93 (s, 3 H, -CH_3^3), 1.25 (t, *J* = 7.2 Hz, 3 H, -$CO_2CH_2CH_3$), 1.16 (t, *J* = 7.6 Hz, 3 H, -CH_2CH_3). IR (KBr, ν, cm^{-1}): 3 360 (NH), 1 740 (ester C = O), 1 670 (lactam C = O), 1 630 (C = C). UV-VIS (CH_2Cl_2), λ_{max}, nm (ε): 403 (24 300); (*Me*OH), 412 (26 100).

Xanthobilirubinic Acid n-Propyl Ester (**1e**)

Prepared according to the general procedure with 88% yield. M.p. = 177 °C. HPLC (C18): R_t = 6.8 min.

^{1}H-NMR ($CDCl_3$, δ, ppm): 11.19 (s, 1H, lactam NH), 10.24 (s, 1H, pyrrole NH), 6.09 (s, 1H, = CH-), 4.00 (t, J = 6.7 Hz, 2H, -CO_2CH_2-), 2.8–2.2 (m, 6H, -CH_2CH_2-, -CH_2CH_3), 2.37 (s, 3H, -$CH_3^{3'\text{ or }5'}$), 2.10 (s, 3H, -$CH_3^{5'\text{ or }3'}$), 1.91 (s, 3H, -CH_3^3), 1.63 (m, 2H, -$CO_2CH_2CH_2$-), 1.15 (t, J = 7.2 Hz, 3H, -CH_2CH_3), 0.90 (t, J = 7.5 Hz, 3H, -$CO_2CH_2CH_2CH_3$). IR (KBr, ν, cm^{-1}): 3370 (NH), 1740 (ester C = O), 1685 (lactam C = O), 1640 (C = C). UV-VIS (CH_2Cl_2), λ_{max}, nm (ε): 403 (23600); (*Me*OH), 412 (25000).

Xanthobilirubinic Acid n-Butyl Ester (**1f**)

Prepared according to the general procedure with 51% yield. M.p. = 115 °C. HPLC (C18): R_t = 7.5 min.

^{1}H-NMR ($CDCl_3$, δ, ppm): 11.09 (s, 1H, lactam NH), 10.12 (s, 1H, pyrrole NH), 6.09 (s, 1H, = CH-), 4.03 (t, J = 6.6 Hz, 2H, -CO_2CH_2-), 2.8–2.2 (m, 6H, -CH_2CH_2-, -CH_2CH_3), 2.36 (s, 3H, -$CH_3^{3'\text{ or }5'}$), 2.10 (s, 3H, -$CH_3^{5'\text{ or }3'}$), 1.93 (s, 3H, -CH_3^3), 1.57 (m, 4H, -$CO_2CH_2CH_2CH_2CH_3$), 1.15 (t, J = 7.8 Hz, 3H, -CH_2CH_3), 0.90 (t, J = 7.8 Hz, 3H, -$CO_2CH_2CH_2CH_2CH_3$). IR (KBr, ν, cm^{-1}): 3360 (NH), 1740 (ester C = O), 1675 (lactam C = O), 1640 (C = C). UV-VIS (CH_2Cl_2), λ_{max}, nm (ε): 403 (17600); (*Me*OH), 412 (20300).

Xanthobilirubinic Acid n-Decyl Ester (**1g**)

Prepared according to the general procedure with 39% yield (62% when *DMF* was used instead of dioxane). M.p. = 79 °C. HPLC (C18): R_t = 19.6 min.

^{1}H-NMR ($CDCl_3$, δ, ppm): 11.07 (s, 1H, lactam NH), 10.16 (s, 1H, pyrrole NH), 6.09 (s, 1H, = CH-), 4.03 (t, J = 7.8 Hz, 2H, -CO_2CH_2-), 2.7–2.2 (m, 6H, -CH_2CH_2-, -CH_2CH_3), 2.36 (s, 3H, -$CH_3^{3'\text{ or }5'}$), 2.12 (s, 3H, -$CH_3^{5'\text{ or }3'}$), 1.93 (s, 3H, -CH_3^3), 1.3–1.2 (m, 16H, -$CO_2CH_2(CH_2)_8CH_3$), 1.15 (t, J = 7.8 Hz, 3H, -CH_2CH_3), 0.87 (t, J = 7.8 Hz, 3H, -$CO_2(CH_2)_9CH_3$). IR (KBr, ν, cm^{-1}): 3360 (NH), 1740 (ester C = O), 1665 (lactam C = O), 1635 (C = C). UV-VIS (CH_2Cl_2), λ_{max}, nm (ε): 402 (10300); (*Me*OH), 413 (9400).

Xanthobilirubinic Acid n-Hexadecyl Ester (**1h**)

This ester could not be obtained by the above procedure. The properties given here correspond to the material prepared from *XBR* tetra-*n*-butyl ammonium and cetyl alcohol tosylate [6]. M.p. = 86 °C.

^{1}H-NMR ($CDCl_3$, δ, ppm): 11.26 (s, 1H, lactam NH), 10.33 (s, 1H, pyrrole NH), 6.09 (s, 1H, = CH-), 4.04 (t, J = 6.6 Hz, 2H, -CO_2CH_2-), 2.84–2.2 (m, 6H, -CH_2CH_2-, -CH_2CH_3), 2.24 (s, 3H, -$CH_3^{3'\text{ or }5'}$), 2.12 (s, 3H, -$CH_3^{5'\text{ or }3'}$), 1.91 (s, 3H, -CH_3^3), 1.35 (m, 28H, -$CO_2CH_2(CH_2)_{14}CH_3$), 1.15 (t, J = 7.5 Hz, 3H, -CH_2CH_3), 0.87 (t, J = 6.4 Hz, 3H, -$CO_2(CH_2)_{14}CH_3$). UV-VIS (CH_2Cl_2), λ_{max}, nm (ε): 402 (8800).

Xanthobilirubinic Acid Benzyl Ester (**1i**)

Prepared according to the general procedure with 25% yield. M.p. = 146 °C. HPLC (C18): R_t = 5.5 min.

^{1}H-NMR ($CDCl_3$, δ, ppm): 11.18 (s, 1H, lactam NH), 10.24 (s, 1H, pyrrole NH), 7.30 (s, 5H, H^{arom}), 6.12 (s, 1H, = CH-), 5.09 (s, 2H, -CO_2CH_2-), 2.9–2.2 (m, 6H, -CH_2CH_2-, -CH_2CH_3), 2.36 (s, 3H, -$CH_3^{3'\text{ or }5'}$), 2.10 (s, 3H, -$CH_3^{5'\text{ or }3'}$), 1.90 (s, 3H, -CH_3^3), 1.16 (t, J = 8.9 Hz, 3H, -CH_2CH_3). IR (KBr, ν, cm^{-1}): 3360 (NH), 1735 (ester C = O), 1680 (lactam C = O), 1630 (C = C). UV-VIS (CH_2Cl_2), λ_{max}, nm (ε): 398 (13400); (*Me*OH), 412 (14300).

Xanthobilirubinic Acid Isobutyl Ester (**1 j**)

Prepared according to the general procedure (detaching mixture was not homogeneous) with 69% yield. M. p. = 178 °C. HPLC (C18): R_t = 6.0 min.

^{1}H-NMR ($CDCl_3$, δ, ppm): 11.13 (s, 1 H, lactam NH), 10.27 (s, 1 H, pyrrole NH), 6.12 (s, 1 H, = CH-), 3.82 (d, J = 6.6 Hz, 2 H, -CO_2CH_2-), 2.8 – 2.2 (m, 6 H, -CH_2CH_2-, -CH_2CH_3), 2.42 (s, 3 H, -$CH_3^{3' \text{ or } 5'}$), 2.15 (s, 3 H, -$CH_3^{5' \text{ or } 3'}$), 1.94 (s, 3 H, -CH_3^3), 1.19 (t, J = 7.8 Hz, 3 H, -CH_2CH_3), 0.93 (d, J = 7.8 Hz, 6 H, -$CO_2CH_2CH(CH_3)_2$). IR (KBr, ν, cm^{-1}): 3 360 (NH), 1 735 (ester C = O), 1 675 (lactam C = O), 1 635 (C = C). UV-VIS (CH_2Cl_2), λ_{max}, nm (ε): 403 (20 000); (*Me*OH), 411 (21 400).

Xanthobilirubinic Acid Neopentyl Ester (**1 k**)

Prepared according to the general procedure (detaching mixture was not homogeneous) with 38% yield. M. p. = 156 °C. HPLC (C18): R_t = 6.6 min.

^{1}H-NMR ($CDCl_3$, δ, ppm): 10.9 (s, 1 H, lactam NH), 10.02 (s, 1 H, pyrrole NH), 6.09 (s, 1 H, = CH-), 3.75 (s, 2 H, -CO_2CH_2-), 2.8 – 2.2 (m, 6 H, -CH_2CH_2-, -CH_2CH_3), 2.36 (s, 3 H, -$CH_3^{3' \text{ or } 5'}$), 2.12 (s, 3 H, -$CH_3^{5' \text{ or } 3'}$), 1.91 (s, 3 H, -CH_3^3), 1.15 (t, J = 7.8 Hz, 3 H, -CH_2CH_3), 0.90 [s, 9 H, -$CO_2CH_2C(CH_3)_3$]. IR (KBr, ν, cm^{-1}): 3 360 (NH), 1 740 (ester C = O), 1 665 (lactam C = O), 1 635 (C = C). UV-VIS (CH_2Cl_2), λ_{max}, nm (ε): 403 (20 000); (*Me*OH), 411 (19 300).

Xanthobilirubinic Acid Isopropyl Ester (**1 l**)

Prepared according to the general procedure (detaching mixture was not homogeneous) with 4% yield. M. p. = 139 °C. HPLC (C18): R_t = 5.9 min. The main detachment products were the free acid **1 a** and its "dimer", mesobilirubin XIII-α.

^{1}H-NMR ($CDCl_3$, δ, ppm): 11 (s, 1 H, lactam NH), 10.04 (s, 1 H, pyrrole NH), 6.10 (s, 1 H, = CH-), 5 (m, 1 H, -$CO_2CH(CH_3)_2$), 2.8 – 2.2 (m, 6 H, -CH_2CH_2-, -CH_2CH_3), 2.35 (s, 3 H, -$CH_3^{3' \text{ or } 5'}$), 2.10 (s, 3 H, -$CH_3^{5' \text{ or } 3'}$), 1.90 (s, 3 H, -CH_3^3), 1.25 (d, J = 7.2 Hz, 6 H, -$CH(CH_3)_2$), 1.15 (t, J = 7.5 Hz, 3 H, -CH_2CH_3). IR (KBr, ν, cm^{-1}): 3 360 (NH), 1 730 (ester C = O), 1 680 (lactam C = O), 1 635 (C = C). UV-VIS (CH_2Cl_2), λ_{max}, nm (ε): 406 (10 500); (*Me*OH), 412 (10 300).

Xanthobilirubinic Acid Ethyleneglycol Monoester (**1 o**)

Prepared according to the general procedure with 65% yield, together with the diester **1 p** (21%, see below). They can be separated by preparative thin layer chromatography (SiO_2; $CHCl_3$: *Me*OH; 10 : 1; R_f = 0.5, **1 o**; 0.39, **1 p**). M. p. = 206 – 209 °C.

^{1}H-NMR ($CDCl_3$, δ, ppm): 11.23 (s, 1 H, lactam NH), 10.30 (s, 1 H, pyrrole NH), 6.12 (s, 1 H, = CH-), 4.21 (m, 2 H, -CO_2CH_2-), 3.80 (m, 2 H, -CH_2OH), 2.8 – 2.4 (m, 6 H, -CH_2CH_2-, -CH_2CH_3), 2.41 (s, 3 H, -$CH_3^{3' \text{ or } 5'}$), 2.14 (s, 3 H, -$CH_3^{5' \text{ or } 3'}$), 1.94 (s, 3 H, -CH_3^3), 1.17 (t, 3 H, -CH_2CH_3). IR (KBr, ν, cm^{-1}): 3 450 (broad, OH), 3 360 (NH), 1 735 (ester C = O), 1 680 (lactam C = O), 1 630 (C = C). UV-VIS (CH_2Cl_2), λ_{max}, nm (ε): 401 (24 400); (*Me*OH), 411 (23 600). MS (electron impact) *m/e* (%): 346 (M^+).

Xanthobilirubinic Acid Ethyleneglycol Diester (**1 p**)

Prepared according to the general procedure with 21% yield, together with the monoester **1 o** (65%, see above). They can be separated by preparative thin layer chromatography (SiO_2; $CHCl_3$: *Me*OH; 10 : 1; R_f = 0.5, **1 o**; 0.39, **1 p**). M. p. = 207 – 211 °C.

^{1}H-NMR ($CDCl_3$, δ, ppm): 11.19 (s, 2 H, 2 × lactam NH), 10.27 (s, 2 H, 2 × pyrrole NH), 6.13 (s, 2 H, 2 × = CH-), 3.68 [s, 4 H, -(-CO_2CH_2-)$_2$-], 2.8 – 2.4 (m, 12 H, 2 × -CH_2CH_2-, 2 × -CH_2CH_3), 2.41 (s, 6 H, 2 × -$CH_3^{3' \text{ or } 5'}$), 2.14 (s, 6 H, 2 × -$CH_3^{5' \text{ or } 3'}$), 1.94 (s, 6 H, -2 × CH_3^3), 1.17 (t, 6 H, 2 × -CH_2CH_3). IR (KBr, ν, cm^{-1}): 3 350 (NH), 1 735 (ester C = O), 1 675 (lactam C = O), 1 635 (C = C).

UV-VIS (CH_2Cl_2), λ_{max}, nm (ε): 401 (47 600); (*Me*OH), 410 (48 000). MS (electron impact) *m/e* (%): 316 ($M^+/2 + 1$).

Xanthobilirubinic Acid Methylamide (**2 a**)

Prepared (75% yield) as a variation of the general procedure used for the synthesis of esters. Detachment involves (4 × 1 h) treatment with 4 *N* solutions of the respective amine in dioxane (see above for preparation). Work up involves solvent evaporation (abundant foam is formed) and eventual purification, by column chromatography, from methyl ammonium bromide (from benzyl bromide residues of the resin). M. p. = 275 – 290 °C (with decomposition). HPLC (C18): R_t = 5.5 min.

^{1}H-NMR ($CDCl_3$, δ, ppm): 10.9 (s, 1 H, lactam NH), 10.0 (s, 1 H, pyrrole NH), 7 (s, 1 H, amide NH), 6.1 (s, 1 H, = CH-), 2.8 – 2.1 (m, 6 H, -CH_2CH_2-, -CH_2CH_3), 2.74 + 2.72 (2 × s, 3 H, *syn* + *anti* N-CH_3), 2.33 (s, 3 H, -$CH_3^{3' \text{ or } 5'}$), 2.1 (s, 3 H, -$CH_3^{5' \text{ or } 3'}$), 1.9 (s, 3 H, -CH_3^3), 1.14 (t, J = 7.8 Hz, 3 H, -CH_2CH_3). IR (KBr, ν, cm^{-1}): 3 340 (NH), 1 710 (amide C = O), 1 680 (lactam C = O), 1 640 (C = C). UV-VIS (CH_2Cl_2), λ_{max}, nm (ε): 403 (30 000); (*Me*OH), 410 (36 000).

Xanthobilirubinic Acid Dimethylamide (**2 b**)

Prepared (65% yield) as described above for the N-methyl amide **2 a**. M. p. = 220 – 225 °C. HPLC (C18): R_t = 6.4 min. Additional spectroscopic data as reported in Ref. [5 c].

Xanthobilirubinic Acid Methylbenzylamide (**2 c**)

Prepared (30% yield) as described above for the N-methyl amide **2 a**. HPLC (C18): R_t = 5.7 min. Additional spectroscopic data as reported in Ref. [5 d].

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