(silica gel, C_6H_6/EtOAc 9:1) 0.11 g of oily N-benzyl, N-(*cis-3*-phenylallyl)-toluenesulfonamide (**5**). – IR. (Nujol): 1350, 1170, no band at 940. – ^{1}H–NMR. (100 MHz): 2.41 (3 H, *s*); 3.98 (2 H, *d* × *d*, J = 2 Hz and 6.5 Hz); 4.26 (2 H, *s*); 5.38 (1 H, *d* × *t*, J = 11.5 Hz and 6.5 Hz); 6.42 (1 H, *d* × *t*, J = 11.5 Hz and 1.5 Hz); 6.8–7.4 (12 H); 7.66 (2 H, *d*, J = 8 Hz).

N-Benzyl, N-(trans-*3-phenylallyl)-toluenesulfonamide* (**6**). Following the procedure described for the preparation of N-(2-phenylallyl), N-(*trans*-3-phenylallyl)-toluenesulfonamide (**1**) [1] 0.5 g of N-(*trans*-3-phenyl-2-propenyl)-trifluoroacetamide was alkylated with benzylbromide to give 0.9 g of crude N-benzyl, N-(*trans*-3-phenylallyl)-trifluoroacetamide. After saponification the resulting N-benzyl, N-(*trans*-3-phenylallyl)-amine was converted to its crystalline hydrochloride, m.p. 209–212° (0.25 g after crystallisation from methanol/ether). Treatment of the amine-hydrochloride (0.25 g) with 0.27 g of toluenesulfonyl chloride and 0.4 g of pyridine followed by the usual workup furnished after crystallisation from ether/hexane 0.054 g of crystals: m.p.: 78–80°. – IR. (Nujol): 1350, 1170, 940. – ^{1}H–NMR. (100 MHz): 2.41 (3 H, *s*); 3.88 (2 H, *d*, J = 6.5 Hz); 4.36 (2 H, *s*); 5.74 (1 H, *d* × *t*, J = 16 Hz and 6.5 Hz); 6.2 (1 H, *d*, J = 16 Hz); 7.0–7.5 (12 H); 7.75 (2 H, *d*, J = 8 Hz).

Thermolysis Experiments (Table 1). 0.04 to 0.25 g of purified compound **1a**, **1b**, **2**, **3**, **5** and **6**, respectively, was heated in 5 ml of refluxing *o*-dichlorobenzene (runs 1–7), or in toluene, using a sealed tube (runs 8–9) for the indicated time. After evaporation and chromatographic removal of apolar and strongly polar impurities (silica gel/benzene) the recovered mixture was analysed by ^{1}H–NMR. spectroscopy (runs 1, 2, 5 and 6). In the experiments run 3, 4, 7, 8 and 9 chromatography of the crude reaction mixture (silica gel/benzene/pentane) afforded 2 fractions (the first one containing the less polar dienes **1a** and **1b** and the second one containing the adducts **2** and **3**), each of which was subjected to ^{1}H–NMR. analysis. From the mixture obtained in run 2 all 3 components **1a**, **2** and **3** were isolated by chromatography and crystallisation and identified by comparison of their ^{1}H–NMR. spectra and melting points.

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287. Synthesis of New Xanthones, I

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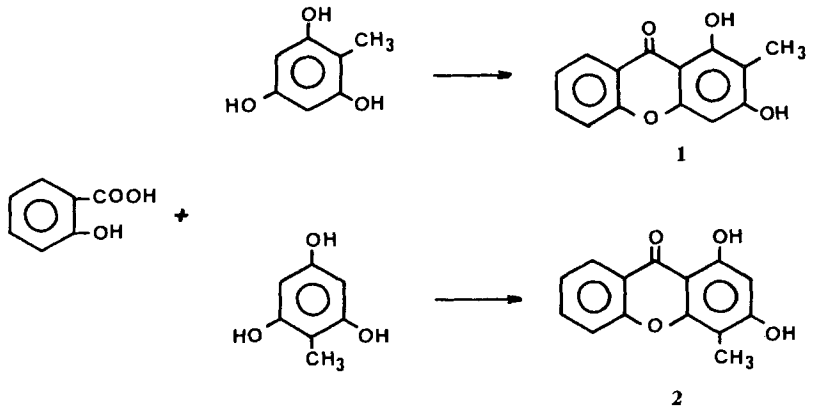
(17. X. 74)

Summary. Condensation of salicylic acid and C-methylphloroglucinol gave the already known 1,3-dihydroxy-2-methylxanthone (**1**) along with two new compounds: 1,3-dihydroxy-4-methylxanthone (**2**) and a second one tentatively presented as being 1,3-dihydroxy-2-methyl-4-(2-hydroxybenzoyl)xanthone (**3**). The UV., IR., NMR. and mass spectra for the two first compounds

are reported and their structures discussed on the basis of δ-values for H(2), H(4), $CH_3(4)$ and $CH_3(2)$. The UV. and IR. spectra for the third compound are reported too.

In 1969 *Jain et al.* [1] described two methods for the synthesis of 1,3-dihydroxy-2-methylxanthone, one of them concerning the condensation of salicylic acid with C-methylphloroglucinol. Obviously, there are two possibilities for this condensation and we can expect that two isomeric compounds may be formed: 1,3-dihydroxy-2-methylxanthone (**1**) and 1,3-dihydroxy-4-methylxanthone (**2**) (*cf. Scheme 1*).

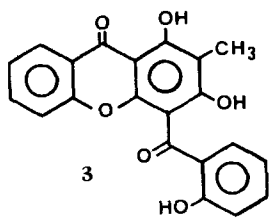
Scheme 1



Jain et al. [1] refer to these two possibilities but claim that the normal course of the reaction corresponds to the formation of the 2-methyl derivate since they have obtained only 2-methyl compounds in the synthesis of several xanthones.

In 1970 one of us [2] described the obtention of this type of compounds but then it was not possible to localise the methyl group. In this paper we report on the obtention of the two isomeric compounds **1** and **2**, though in very different yields (100:2), using the method described by *Grover et al.* [3] and employing almost stoichiometric amounts of salicylic acid and C-methylphloroglucinol. In our experimental conditions we have also obtained another xanthonic substance that seems to result from condensation of **1** with salicylic acid, as we think to have confirmed by direct reaction of these two compounds. The compound is still under study and we tentatively ascribed for it the structure **3** (*cf. Scheme 2*).

Scheme 2



The product resulting from condensation of salicylic acid and C-methylphloroglucinol shows in TLC. (chloroform/acetone 95:5) several immobile substances and three spots $FeCl_3$-positive with Rf values *ca.* 0.4 (**1**), 0.3 (**2**) and 0.7 (**3**). After their isolation and crystalization, **1** and **2** show different m.p., IR., and UV. spectra and the same M.W. in the MS. The m.p. of **1** agrees with that one recorded by *Jain et al.* [1] for the 2-methyl derivate, the structure of which having been established by those authors by comparing the chemical shifts concerning the methyl group of similar compounds prepared by them.

The chemical shifts observed in the compounds that we have obtained are indicated in *Table 1* for the isolated and methylic protons in the substituted rings:

Table 1. *NMR. spectral data in* CD_3COCD_3 (δ in ppm)

	H(2) or H(4)	CH_3(2) or CH_3(4)
1	6.52 *s*	2.10 *s*
2	6.35 *s*	2.26 *s*

The difference between the δ-values for the two H can not be considered as a great one, but is possible to make a comparison with similar compounds refered in literature. So, *Lewis et al.* [4] found, in the same solvent, for 1,3,5- and 1,3,7-trihydroxyxanthone $\delta = 6.28$ and 6.26 for H(2) and $\delta = 6.50$ and 6.40 for H(4), respectively.

Looksley et al. [5] recorded also in CD_3COCD_3 $\delta = 6.23$ and 6.29 for H(2) and $\delta = 6.38$ and 6.46 for H(4), in 1,3-dihydroxy-7-methoxy and 1-hydroxy-3,7-dimethoxyxanthones. In other solvents and with 1,2,3- and 1,3,4-substituted xanthones, the δ-values for H(4) are practically always greater than for H(2) [6–14]. On other hand, the calculated chemical shifts [15] for H(4) and H(2) in **1** and **2** are very closed to the experimental ones (*Table 2*), the small differences between the two sets being due probably to steric effects caused by the methyl group.

Table 2. *NMR. spectral data* (δ in ppm)

	calculated [15]	experimental
H(4) in **1**	6.44	6.52
H(2) in **2**	6.26	6.35

At last, we can consider that δ-values for CH_3 in **1** and **2** (2.10 and 2.26, respectively) agree with *Jain et al.*'s values [1] for several 2(or 4)-methyl-1-hydroxy-3-methoxyxanthones, in CD_3Cl: 1.92 and 1.99 for 2-CH_3 and 2.11 and 2.13 for 4-CH_3.

The experimental data support the two theorical routes for the condensation of salicylic acid with C-methylphloroglucinol, the poor yield for the 4-CH_3 derivate being perhaps justified by steric reasons.

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Experimental Part

All m.p. were taken in a *Kofler* microscope and are uncorrected. UV. spectra were recorded on a *Bausch & Lomb-Spectronic* 505, in Methanol. IR. spectra were recorded on a *Perkin-Elmer* 257, in KBr, and only the major bands are quoted. MS. were obtained on a *Hitachi* RMU-6M. NMR. spectra were obtained on a 60 MHz *Hitachi* R32, in CD_3COCD_3. Analytical and preparative TLC. were made on Kieselgel HF_{254} *Merck* (Type 60), activated plates at 110°/30 min, in chloroform/acetone 95:5. The following weights correspond to average values of several preparations.

A mixture of salicylic acid (1.0 g), C-methylphloroglucinol[1]) (1.2 g), fused $ZnCl_2$ (3 g) and $POCl_3$ (7 ml) was heated at 70° for 3 h and, after cooling, poured over ice. After 12 h at room temperature the resultant red solid was separated by centrifugation and washed with cold and boiling water until the washing liquids were colourless. TLC. of the dry product shew some immobile components and, among others, 3 spots $FeCl_3$-positive and visible under UV. light (254 nm) with Rf *ca.* 0.4 (very strong), 0.3 (slight) and 0.7 (very slight). The sublimation (190–210°/1 Torr) of the red powder (1.5 g) gave a yellow product (0.8 g), that was washed with hot water and, after drying, shew the same 3 spots only in TLC. The product (1 g) was extracted with methanol till this one was colourless and the residual part (15 mg), crystallized from cloroform/acetone as white-yellowish needles (12 mg) (**3**), gave only one spot in TLC. (Rf *ca.* 0.7). The concentration of the methanolic extract afforded yellow needles (500 mg after crystallization from methanol) giving only one spot in TLC. (Rf *ca.* 0.4) (**1**). The TLC. of the mother liquors shew 2 spots (**1** and **2**) wich were separated by preparative TLC. (application in acetonic solution; 18–20 plates, 20 × 20 cm). The silicagel corresponding to **2** was extracted with 0.1N NaOH and the alkaline solution acidified with 5N HCl. The resultant insoluble product was separated by centrifugation, washed with water and dried at 40°. After an ether extraction, this solvent was evaporated and the residue crystallized from methanol as yellow needles (10 mg) (**2**) giving only one spot in TLC. (Rf *ca.* 0.3).

1,3-dihydroxy-2-methylxanthone (**1**). M.p. = 250–251°; $FeCl_3$-positive; UV. [λ_{max} (log ε)]: 216 (4.38), 238 (4.48), 255 (sh.), 312 (4.18), *ca.* 352 (3.64); λ_{min} 223 (4.29), 248 (sh.), 272 (3.71) nm. – IR.: ν_{max} (cm^{-1}): 3100, 1640, 1610, 1560, 1485, 1465, 1370, 1330, 1290, 1230, 1210, 1180, 1155, 1140, 1100, 940, 875, 830, 820, 760, 680. – MS., M^+ = 242 (100%), *m/e* (%) 243 (16), 241 (37), 214 (10), 213 (32), 197 (5), 187 (12), 185 (7), 168 (6), 139 (11), 129 (5), 128 (11), 127 (6), 121 (12), 103 (5), 102 (6), 93 (7), 92 (11), 91 (5), 77 (18), 76 (9), 75 (9), 74 (7), 69 (10), 65 (15), 64 (10), 63 (16), 62 (6), 55 (13), 53 (11), 51 (11), 50 (8), 39 (14), 27 (8); *m**: 161 (213 → 185); *m**: 189 (242 → 214); *m**: 207 (242 → 224). – NMR.: 2.10 (*s*, CH_3(2); 3.15 (*s*, OH; 6.53 (*s*, H(4)); 7.35–8.30 (*m*, H(5), H(6), H(7), H(8)).

1,3-dihydroxy-4-methylxanthone (**2**). M.p. = 241–242°; $FeCl_3$-positive; UV. [λ_{max} (log ε)]: 212 (4.29), 236 (4.44), 260 (4.35), 312 (4.08), *ca.* 362 (3.68); λ_{min} 221 (4.24), 248 (4.23), 278–280 (3.88), 343 (3.69) nm. – IR. ν_{max} (cm^{-1}): 3175, 1650, 1610, 1590, 1570, 1520, 1490, 1475, 1415, 1380, 1345, 1310, 1280, 1230, 1190, 1150, 1100, 1015, 940, 900, 845, 805, 755, 720, 690, 620. – MS.: M^+ = 242 (100%), *m/e* (%) 243 (18), 241 (38), 223 (6), 214 (10), 213 (47), 199 (6), 197 (8), 185 (22), 184 (6), 172 (6), 171 (14), 168 (10), 167 (12), 165 (11), 157 (14), 155 (6), 147 (38), 141 (12), 140 (6), 139 (34), 137 (15), 136 (6), 131 (10), 129 (32), 128 (64), 127 (36), 126 (10), 122 (6), 121 (50), 120 (14), 117 (6), 116 (10), 115 (58), 114 (13), 113 (15), 111 (6), 110 (6), 109 (8), 108 (6), 105 (13), 104 (15), 103 (18), 102 (26), 101 (16), 99 (9), 98 (9), 94 (6), 93 (37), 92 (80), 91 (28), 90 (13), 89 (42), 88 (19), 87 (28), 86 (16), 83 (8), 81 (13), 80 (8), 79 (40), 78 (25), 77 (165), 76 (69), 75 (67), 74 (54), 73 (6), 70 (10), 69 (131), 68 (8), 67 (19), 66 (26), 65 (104), 64 (83), 63 (148), 62 (57), 61 (14), 56 (42), 54 (12), 53 (94), 52 (34), 51 (111), 50 (104), 49 (6), 45 (7), 43 (29), 42 (39), 41 (31), 40 (18), 39 (161), 38 (47), 37 (11), 29 (43), 27 (54), 26 (11); *m**: 161 (213 → 185); *m**: 189 (242 → 214). – NMR.: 2.26 (*s*, CH_3(4)); 3.00 (*s*, OH); 6.35 (*s*, H(2)); 7.25–8.25 (*m*, H(5), H(6), H(7), H(8)).

1,3-dihydroxy-2-methyl-4-(2-hydroxybenzoyl)xanthone (**3**). M.p. = 216–217°; $FeCl_3$-positive; UV. [λ_{max} (log ε)]: 211 (4.61), 238 (4.56), 255 (sh), 310 (4.22), 359 (3.61); λ_{min} 222 (4.40), 248 (sh.), 272 (3.80), 345 (3.61) nm. – IR. [ν_{max} (cm^{-1})]: 3170, 2960, 1680, 1625, 1610, 1580, 1490, 1480, 1460, 1440, 1405, 1390, 1380, 1335, 1300, 1250, 1230, 1210, 1190, 1170, 1155, 1130, 1115, 1100, 1050, 1035, 885, 870, 820, 800, 760, 700, 675. – MS.: M^+ = 362 (100%).

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288. Totalsynthese von Humaninsulin unter gezielter Bildung der Disulfidbindungen

Vorläufige Mitteilung[1][2]

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(20. XI. 74)

Summary. A preliminary account is given of a total synthesis of human insulin involving directed formation of the three disulfide bonds at different stages of the fragment-condensation approach. The synthesis was facilitated by the application of two new methods for the selective removal of protecting groups. In the first, two S-Trt-protected cysteine residues are converted to the disulfide without affecting S-Acm-protected cysteine residues. The second new method consists in a very mild, pH-controlled, acidolysis of N(α)-Trt, leaving intact N(α)-Bpoc and other acid-labile protecting groups. The last step of the synthesis was the formation of the disulfide bridge between the Acm-protected cysteine residues A7 and B7 by iodine. Extensive counter-current distribution yielded the synthetic hormone in pure form. It was compared and found to be identical with natural human insulin. Identification was achieved by means of thinlayer chromatography and electrophoretic procedures, as well as by comparing the pattern of breakdown by enzymes (finger-printing). The natural and synthetic hormones were crystallized under identical conditions. The synthetic human insulin was found to possess full biological activity in an *in vitro* system.

[1] Eine ausführliche Beschreibung soll später in dieser Zeitschrift erfolgen.

[2] Zu der hier verwendeten, abgekürzten Schreibweise für Aminosäuren, Peptide und ihre Derivate vgl. [1]; ferner bedeuten: Acm-: Acetamidomethyl-[2], Boc-: *t*-Butyloxycarbonyl-Bpoc-: 2-(*p*-Biphenylyl)-isopropyloxycarbonyl-[3], But: *t*-Butyl-, HOBt: 1-Hydroxybenzotriazol, TFA: Trifluoressigsäure, TFEt: Trifluoräthanol, Trt-: Triphenylmethyl-, MV.: multiplikative Verteilung, K = Verteilungs-Koeffizient.