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Solubilization of Certain Organic Compounds by Use of Isocyanato Esters

W. J. HUMPHLETT AND C. V. WILSON

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A new procedure for the solubilization of many types of organic molecules carrying one or more hydroxy, carboxy, or amino groups is described. Besides simple long-chain alcohols and acids which lead to surfactants, such substances as the sterols, vitamins, dyes, optical bleaches, etc., have been made water-soluble. The method consists, essentially, in treating isocyanato esters with molecules containing one or more of the above-named functional groups, and selectively hydrolyzing the ester group to the alkali salt of the corresponding acid.

Broadly speaking, organic compounds may be classified as water-soluble or water-insoluble. The soluble compounds frequently are salts derived by neutralization of acidic (sulfo, sulfato, carboxy, hydroxy) or basic (amino) groups in the molecule. These are, of course, supplemented by the nonionic, exemplified by the polyhydroxy compounds (glycerin, sugars) and, more recently, the polyoxyethyl derivatives of a great variety of alcohols, amines, acids, and phenols. While sulfonation or sulfation imparts the greatest solubility, these groups may often be undesirable for various reasons. The use of the carboxy group is often of considerable value but direct carboxylation is not a generally convenient reaction and such acids are usually built up stepwise.

An indirect method for introducing carboxy groups has recently been devised in these Laboratories. Briefly, it consists in treating an alcohol, phenol, amine, or carboxy acid under anhydrous conditions with any one of the isocyanato esters derived from the amino acids, as already described.[1] The product (urethane-, urea-, or amide-ester) is then selectively hydrolyzed to yield the mono-, di- or polycarboxylic acid, usually as the sodium or potassium salt. The urethane, urea or amide linkage established by the isocyanato group is much more resistant to hydrolysis. By this procedure many substances having low solubility in water can be converted to water-soluble products. The reactions may be illustrated by the following general equations:

$$\mathrm{ROH} + \mathrm{OCNCHR'COOR''} \longrightarrow \mathrm{ROCONHCHR'COOR''} \longrightarrow \mathrm{ROCONHCHR'COONa} \quad \text{(A)}$$

$$\mathrm{RNH_2} + \mathrm{OCNCHR'COOR''} \longrightarrow \mathrm{RNHCONHCHR'COOR''} \longrightarrow \mathrm{RNHCONHCHR'COONa} \quad \text{(B)}$$

$$\mathrm{RCOOH} + \mathrm{OCNCHR'COOR''} \longrightarrow \mathrm{RCONHCHR'COOR''} \longrightarrow \mathrm{RCONHCHR'COONa} \quad \text{(C)}$$

Solubilization by such a procedure may have valuable application in many fields. Long-chain alcohols, amines or acids, for example, yield water-soluble compounds with excellent surface-active properties. The product (I) derived from lauryl alcohol and ethyl isocyanatoacetate, followed by selective hydrolysis, is more soluble than lauric

$$\mathrm{C_{12}H_{25}OCONHCH_2COONa}$$

I

$$\mathrm{C_{12}H_{25}OCONHCHCOONa}$$
$$\mathrm{CH_2CH_2COONa}$$

II

acid. A still more soluble compound (II) results if dimethyl isocyanatoglutarate is substituted for the isocyanatoacetate. Many nonionic materials, such as *p-t*-octylphenoxytetraethoxyethanol[2] can be converted to anionic materials by this reaction. Soluble urea derivatives such as III, derived from laurylmethylamine and diethyl isocyanatosucci-

$$n\text{-}\mathrm{C_{12}H_{25}N(CH_3)CONHCHCOOH}$$
$$\mathrm{CH_2COOH}$$

III

$$n\text{-}\mathrm{C_{11}H_{23}CONHCHCOOH}$$
$$\mathrm{(CH_2)_2COOH}$$

IV

nate, are easily obtained. The solubilization of long-chain acids proceeds easily. For example, lauric acid yields the product IV, obtained with difficulty by the usual Schotten-Baumann procedure or by a recent method described by Jungermann *et al.*[3]

Many more complex materials, such as the rosin acids, rosin amine,[4] rosin alcohol[4] and the low-molecular-weight polyethylene glycol derivatives of these substances, can be solubilized by this procedure. Abitol,[4] which is described as a mixture

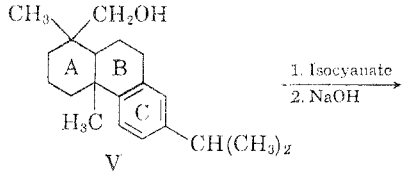
(1) W. J. Humphlett and C. V. Wilson, *J. Org. Chem.*, **26**, 2507 (1961).

(2) Rohm and Haas product, Triton X-45.

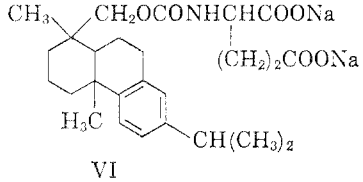
(3) E. Jungermann, J. F. Gerecht, and I. J. Krems, *J. Am. Chem. Soc.*, **78**, 172 (1956).

(4) Obtainable from Hercules Powder Co., Wilmington, Del.

of three closely related alcohols, one of which has the structure V (the others have ring C reduced, and one double bond in ring B, respectively), can be converted to a water-soluble product by treatment with dimethyl isocyanatoglutarate, followed by selective hydrolysis. Structure VI represents



V



VI

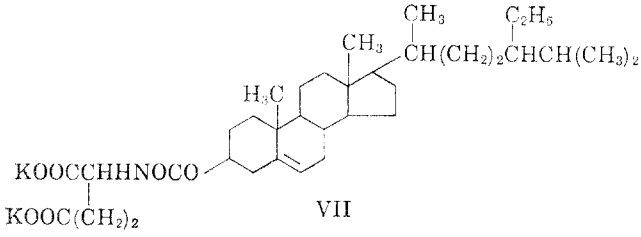
that part of the solubilized material derived from V. Commercial rosin can be solubilized by a similar reaction; the products contain an intermediate amide linkage (see Equation B) rather than the urethane linkage resulting from the alcohols. Since rosin is often used as one of the ingredients of soaps,[5] some of these more soluble derivatives may be of use in the modern detergents.

Since both primary and secondary alcohols react with the isocyanates, the sterol group as a class was investigated. Soluble products were obtained from cholesterol, stigmasterol, β-sitosterol, campesterol, etc.[6] It is of interest that the potassium salts of these substances are usually much more soluble than the sodium or ammonium salts. As an example, the structure of the product obtained from β-sitosterol and dimethyl isocyanatoglutarate is shown in VII. The mixture of soluble soy sterols obtained by this procedure is of considerable interest for use in hypercholesterolemia.[7]

Other substances having physiological activity which contain alcoholic or phenolic functions that can be solubilized by this procedure include Vitamin D_2 (Calciferol), phytol, Vitamin A, and Vitamin E (α-tocopherol).[8] The product (VIII) obtained from Vitamin E and dimethyl isocyanatoglutarate, followed by selective hydrolysis, is a free-flowing powder which is readily soluble in water.

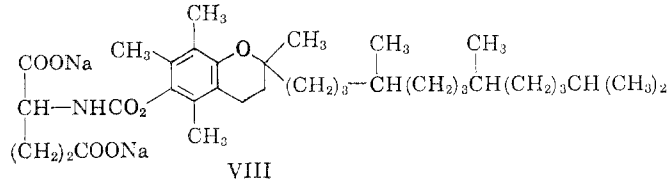
The generality of this reaction may be open to question but it has been established that phenol itself reacts with diethyl isocyanatosuccinate under the same conditions used in the preparation of VIII. Isocyanates derived from α-amino acids are, of course, activated by the carbonyl group of the ester, as discussed previously. The reactivity with phenols would probably be increased further by the use of catalysts such as tertiary amines. Details on the reaction with phenol are included in the experimental section.

Dyes of many types carrying reactive OH or NH_2 groups could be modified by this procedure to yield either the so-called disperse dyes or their water-soluble analogs. Such a pair of dyes (IXa and IXb) was prepared from 1,4-diaminoanthraquinone and dimethyl isocyanatosuccinate. Optical bleaches

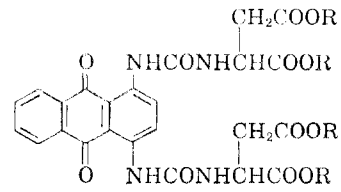


VII

in which water-solubility is bestowed upon the molecule by introduction of the aspartic or glutamic acid residue, rather than by the usual sulfonation, can also be obtained. Such a substance is 3,7-bis(1,3-dicarboxypropylureylene)dibenzothiophene dioxide (sodium salt) (X). Similar substances are available from 4,4″-diamino-*p*-terphenyl and 3-(4-aminophenyl)coumarin.

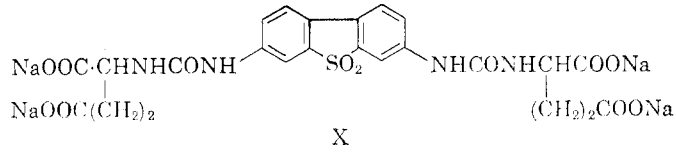


VIII



IXa. R = CH_3
IXb. R = Na

(5) Surface Active Agents, Schwartz and Perry, Interscience, New York (1949), Vol. I, p. 28.
(6) W. J. Humphlett and C. V. Wilson, U. S. Patent 2,875,214 (1959).
(7) D. C. Herting and P. L. Harris, *Federation Proc.*, 19, 18 (1960).
(8) W. J. Humphlett and C. V. Wilson, U. S. Patent 2,875,195 (1959).



X

The ease and completeness with which the isocyanato esters react with compounds having an active hydrogen, particularly as OH or NH_2 groups, make them attractive solubilizing agents. In the medical or pharmaceutical fields, they might be used advantageously, for the amino acids, essential or nonessential, produced by hydrolysis, would have no ill effects upon the human system.

EXPERIMENTAL

Sodium carbolauroxyglycinate (I). *Ethyl carbolauroxyglycinate.* A mixture of 18.6 g. (0.1 mole) of lauryl alcohol and 12.9 g. (0.1 mole) of ethyl isocyanatoacetate (protected from moisture) was allowed to stand overnight and then heated for 3 hr. at 80°. After cooling, 75 ml. of petroleum ether (b.p. 35–60°) was added and the resulting solution was chilled in Dry Ice–acetone. The solid that separated was collected on a chilled funnel and dried in the air; yield, 29 g. (92%). A sample, recrystallized from petroleum ether, melted at 36°.

Anal. Calcd. for $C_{17}H_{33}O_4N$: C, 64.8; H, 10.5; N, 4.4. Found: C, 64.4; H, 10.2; N, 4.6.

Hydrolysis was effected by dissolving 21.5 g. of the ester in 50 ml. of absolute alcohol at 60° and adding thereto 2.8 g. of sodium hydroxide in 3 ml. of water and an additional 25 ml. of alcohol. The sodium salt began to separate almost at once. The mixture was heated on the steam bath for 15 min., cooled to 10° and filtered. The resulting solid was washed with ether and dried; yield, 19 g. (90%). The free acid, carbolauroxyglycine, was obtained in 94% yield by acidification of an aqueous solution of the sodium salt. The crude acid was recrystallized from ether, m.p. 96°.

Anal. Calcd. for $C_{15}H_{29}O_4N$: C, 62.7; H, 10.1; N, 4.9. Found: C, 62.6; H, 10.5; N, 4.6.

Dimethyl carbolauroxyglutamate, the disodium salt (II) and the free acid therefrom were obtained by similar procedures.

Anal. Calcd. for the ester (m.p. 44°, from petroleum ether): $C_{20}H_{37}O_6N$: C, 62.0; H, 9.5; N, 3.6. Found: C, 62.2; H, 9.1; N, 3.8.

Anal. Calcd. for the free acid (m.p. 76°, from ether–petroleum ether): $C_{18}H_{33}O_6N$: C, 60.2; H, 9.2; N, 3.9. Found: C, 60.0; H, 9.1; N, 3.8.

Sodium 1-lauryl-1-methylureidosuccinate (III). *Diethyl 1-lauryl-1-methylureidosuccinate.* To 10.35 g. (0.16 mole) of diethyl isocyanatosuccinate was added, with stirring and cooling, 33.4 g. (0.16 mole) of *N*-methyllaurylamine. The addition was carried out at such a rate that the temperature did not rise above 70°. The mixture was heated at 70–75° for 0.5 hr. after the addition was complete. The mixture solidified on cooling. A small sample recrystallized from hexane melted at 35°.

Anal. Calcd. for $C_{22}H_{42}O_5N_2$: C, 63.7; H, 10.1; N, 6.7. Found: C, 64.0; H, 10.5; N, 6.5.

The ester was converted to the sodium salt by treating it in 100 ml. of water and 50 ml. of ethyl alcohol with 12 g. of sodium hydroxide. The salt (III) was isolated by removal of the solvent. Acidification of a solution of the sodium salt gave the free acid, m.p. 70–72°.

Anal. Calcd. for $C_{18}H_{34}O_5N_2$: C, 60.3; H, 9.5; N, 7.8. Found: C, 60.0; H, 9.4; N, 8.1.

Solubilization of Abitol.[4] To 62 g. of Abitol was added 45 g. of diethyl isocyanatoglutarate. The mixture was warmed slightly. Two layers formed. On further warming and mixing, an exothermic reaction set in, the temperature rising to 165°. After standing for several hours, the product was dissolved in 100 ml. of alcohol and treated with 19 g. of sodium hydroxide dissolved in 19 ml. of water and 400 ml. of alcohol. A solid began to separate at once. The mixture was heated for 1 hr. at 65–70°, cooled to 20° and the solid collected on a filter, washed with alcohol, and dried; yield, 105 g. The product is quite soluble in water and has a high calcium tolerance.

Solubilization of sterols. Potassium carbositosteryloxyglutamate (VII). A solution of 1.5 g. (0.0036 mole) of β-sitosterol (m.p. 134–136°) and 0.66 g. (0.0033 mole) of dimethyl α-isocyanatoglutarate in 25 ml. of xylene was refluxed for 5 hr. and the solvent removed under reduced pressure. The ester was saponified with 0.5 g. of potassium hydroxide in 100 ml. of 45% alcohol. The product, a white, free-flowing powder, amounted to 1.8 g. (80%).

For purification, the potassium salt was dissolved in water and acidified with hydrochloric acid. The free acid, recrystallized twice from ethyl ether, melted at 193°. The pure potassium salt was obtained from the acid by redissolving the latter in alcohol and adding an alcoholic solution of potassium hydroxide (5% excess) thereto. This salt is quite soluble in water, e.g., 1.6 g. dissolved easily in 6 ml. of water. The corresponding sodium salt is only slightly soluble in water.

Several other sterols were solubilized by a similar procedure. Melting points, yields and analyses of various derivatives are collected in Table I.

Solubilization of Vitamin E (VIII). A solution of 40.6 g. (0.09 mole) of α-tocopherol (93.7% α-tocopherol, 95.5% total tocopherols), 16.1 g. (0.08 mole) of dimethyl α-isocyanatoglutarate and 200 ml. of anhydrous xylene was refluxed for 48 hr. After removal of the solvent under reduced pressure, the residual ester was obtained as an orange oil. The ester was saponified by warming with a solution of 7 g. of sodium hydroxide in 200 ml. of 90% alcohol for 45 min. The solid product was collected and washed with acetone; yield, 35.8 g. (69.5%) of a tan powder.

For further purification, the salt was dissolved in 150 ml. of water and the solution extracted with ether. The aqueous phase was separated, warmed with powdered charcoal and filtered. To this solution was added an excess of dilute hydrochloric acid and the precipitated solid acid product was collected and dried. The acid was dissolved in alcohol and the solution warmed with charcoal and filtered. To this solution was added a 5% excess of sodium hydroxide dissolved in alcohol. The precipitated product amounted to 22.1 g. (62% recovery), E(1%, 1 cm.) (283 mμ) = 24.2, m.p. 292.° This and other ultraviolet analyses employed ethanol as a solvent.

To demonstrate the solubility of this product, 1 g. of the salt was dissolved readily in 2 ml. of water.

A solution of the salt gave the corresponding acid upon acidification with hydrochloric acid, E(1%, 1 cm.) (283 mμ) = 35.6, m.p. 107°.

Anal. Calcd. for $C_{35}H_{57}O_7N$: C, 69.7; H, 9.4; N, 2.3. Found: C, 70.2; H, 9.2; N, 2.3.

Analyses in the infrared of both the salt and the acid gave curves having characteristics of the Vitamin E molecule.

By a method identical to that in the foregoing example, 48.8 g. (0.11 mole) of α-tocopherol and 18.7 g. (0.10 mole) of dimethyl α-isocyanatosuccinate were caused to react and subsequently saponified with 8.3 g. of sodium hydroxide; yield, 41.3 g. (66%) of a water-soluble product, m.p. 234°.

The corresponding acid was prepared from the salt, E(1%, 1 cm.) (283 mμ) = 32.7.

Anal. Calcd. for $C_{34}H_{55}O_7N$: C, 69.3; H, 9.4; N, 2.4. Found: C, 69.4; H, 9.4; N, 2.4.

TABLE I

URETHANES DERIVED FROM VARIOUS STEROLS

R—OCONHCHCOOM
(CH$_2$)$_n$COOM

R	n	M	Formula	M.P.	Yield, %	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
		CH_3		120[a]							
β-Sitosteryl	2	K		286	80						
		H	$C_{35}H_{57}O_6N$	192–193[b]		71.5	9.7	2.4	71.7	9.4	2.7
		CH_3		121–122[c]							
Campesteryl	2	K		281	84						
		H	$C_{34}H_{55}O_6N$	197–198[b]		71.2	9.6	2.4	71.3	9.3	2.8
		CH_3	$C_{37}H_{59}O_6N$	124–126[d]		72.3	9.7	2.3	72.0	9.5	2.2
Stigmasteryl	2	K		282	100						
		H	$C_{35}H_{55}O_6N$	203[b]		71.8	9.5	2.4	71.9	9.9	2.5
Cholesteryl	2	CH_3	$C_{35}H_{57}O_6N$	133[d]	99	71.5	9.7	2.4	70.8	9.6	2.5
		Na			97						
		H	$C_{33}H_{53}O_6N$	190–192[e]		70.7	9.5	2.5	70.3	9.7	2.9
		CH_3	$C_{36}H_{57}O_6N$	125[a]		72.1	9.6	2.3	72.3	9.9	2.4
Stigmasteryl	1	K		255	87						

[a] Recrystallized from ethanol. [b] Recrystallized from ether. [c] Recrystallized from methanol. [d] Recrystallized from aqueous ethanol. [e] Recrystallized from acetone/toluene.

Phenyl 1,2-dicarboxyethylcarbamate. A solution of 23.5 g. (0.25 mole) of redistilled phenol and 53.8 g. (0.25 mole) of diethyl isocyanatosuccinate in 300 ml. of anhydrous xylene was refluxed under anhydrous conditions (calcium chloride tube) for 48 hr. The xylene was removed *in vacuo* and the residual product crystallized from aqueous acetone. This crude product (75 g.) was recrystallized twice from ether to give 32 g. of white crystals, m.p. 73°. The urea derived from the above isocyanate has m.p. 80° and gives a marked depression in melting point on admixture with the carbamate.

Anal. Calcd. for $C_{15}H_{19}NO_6$: C, 58.2; H, 6.2; N, 4.5. Found: C, 58.5; H, 6.4; N, 4.6.

Solubilization of Vitamin A. A solution was prepared of 3.33 g. (0.012 mole) of crystalline Vitamin A alcohol (m.p. 63–64°) E(1%, 1 cm.) (325 mμ) = 1820, 2.09 g. (0.01 mole) of dimethyl isocyanatoglutarate, 1.8 ml. of anhydrous pyridine and 23 ml. of anhydrous benzene in a 50-ml. amber flask. The solution was refluxed for 1 hr. 35 min., protected from atmospheric moisture by a calcium chloride tube. After removal of the solvent *in vacuo*, the corresponding urethane-ester was obtained as a viscous oil, E(1%, 1 cm.) (325 mμ) = 990 and having a characteristic carotenoid spectrum in the infrared. To a solution of the ester in 95% ethyl alcohol was added 0.9 g. of sodium hydroxide pellets dissolved in 20 ml. of alcohol and the reaction mixture swirled at room temperature for 30 min. The resulting sodium salt was collected and washed with ethyl alcohol and then ethyl ether, yielding 4.17 g. (83%) of a yellow, free-flowing powder, E(1%, 1 cm.) (325 mμ) = 885, m.p. 360° and having a characteristic carotenoid infrared spectrum.

The solubility of this product was demonstrated by dissolving 2.0 g. of the sodium salt in 5.0 ml. of water, giving a yellow, homogeneous, clear solution.

A solution of the salt yielded the corresponding acid upon addition of dilute hydrochloric acid, E(1%, 1 cm.) (325 mμ) = 765, m.p. 80°.

Anal. Calcd. for $C_{26}H_{37}O_6N$: C, 67.9; H, 8.1; N, 3.0. Found: C, 67.7; H, 8.3; N, 2.9.

By a method identical to that just described, employment of dimethyl α-isocyanatosuccinate (b.p. 65° at 0.5 mm. n_D^{25} 1.4445) in a reaction with crystalline Vitamin A also yielded a water-soluble product, E(1%, 1 cm.) (325 mμ) = 815, m.p. 310°. The water-soluble derivatives of Vitamin A are unstable in solution, losing about one-half of their specific extinction in 4 hr.

Solubilization of Vitamin D_2 (Calciferol). A solution of 5.0 g. (0.013 mole) of Vitamin D_2 [m.p. 114°, E(1%, 1 cm.) (263 mμ) = 467], 2.3 g. (0.011 mole) of dimethyl α-isocyanatoglutarate, 5 ml. of pyridine and 30 ml. of benzene was refluxed for 2 hr. and the solvent removed under reduced pressure. The urethane-ester, obtained as a viscous oil, was dissolved in a solution of 1.58 g. of potassium hydroxide in 95% ethyl alcohol and refluxed for 45 min. The potassium salt, precipitated from the cooled solution, was collected and rinsed with acetone and then with ethyl ether, yielding 6.2 g. (84%) of a white, free-flowing powder, m.p. 240°, E(1%, 1 cm.) (265 mμ) = 208 in water solution. This product is readily soluble in water.

A water solution of the potassium salt was acidified with hydrochloric acid, giving the corresponding acid, m.p. 83°, E(1%, 1 cm.) (263 mμ) = 289.

Anal. Calcd. for $C_{34}H_{51}O_6N$: N, 2.5. Found: N, 2.4.

The sodium salt was prepared by dissolving the corresponding acid in an ethyl alcohol solution containing a slight excess of sodium hydroxide. This product, m.p. 318°, is soluble in water.

The ammonium salt was prepared by dissolving the corresponding acid in ethyl alcohol and adding an excess of concentrated ammonium hydroxide solution. Evaporation under reduced pressure left the solid ammonium derivative, m.p. 180°, E(1%, 1 cm.) (268 mμ) = 210 in water solution. This product is readily soluble in water.

Solubilization of diaminoanthraquinone (IXb). A mixture of 12 g. of 1,4-diaminoanthraquinone and 20 g. of dimethyl isocyanatosuccinate in 75 ml. of chlorobenzene was heated to the boiling point of the solvent under reflux for 1 hr. and allowed to cool. The solid that separated was collected on a filter, washed with alcohol, and dried; yield, 24 g. (75%).

An analytical sample was prepared by recrystallization from alcohol.

Anal. Calcd. for the ester (IXa) $C_{28}H_{28}O_{12}N_4$: C, 54.9; H, 4.6; N, 9.2. Found: C, 55; H, 4.7; N, 9.4.

A solution of 5 g. of the ester in 75 ml. of ethanol was heated to 60–70° and treated with 1.5 g. (about 4 molar equivalents) of sodium hydroxide in 30 ml. of water. The mixture was heated for 15 min. and then poured into alcohol. The aqueous alcohol was decanted from the precipitated oil. The oil was slurried with fresh absolute alcohol, the liquid decanted and the washing repeated until the oil became a granular solid. This sodium salt has high solubility in water. A sample was converted to the free acid by acidification of its aqueous solution with hydrochloric acid. The acid was collected on a filter, taken up in acetone and crystallized therefrom by concentration and cooling.

Anal. Calcd. for $C_{24}H_{20}O_{12}N_4$: C, 51.8; H, 3.6; N, 10.1. Found: C, 51.4; H, 3.4; N, 10.3.

Solubilization of 4,4″-diamino-p-terphenyl. To a solution of 10 g. of 4,4″-diamino-*p*-terphenyl in 300 ml. of boiling chlorobenzene was added 15.5 g. (2 molar equivalents) of dimethyl isocyanatoglutarate. The heating was continued, and within 0.5 hr. the mixture had set to a crystalline mass. After heating for 15 min. more, the mixture was diluted with acetone, slurried, and filtered. The semisolid product was removed from the filter, slurried again in acetone, and again filtered. This was repeated with ether as the diluent. The dry product (15.5 g.) is pure 4,4″-bis(1,3-dicarbomethoxypropylureylene)-*p*-terphenyl, m.p. about 225°.

Anal. Calcd. for $C_{34}H_{38}N_4O_{10}$: C, 61.3; H, 5.7; N, 8.4. Found: C, 61.8; H, 5.9; N, 8.3.

This ester could be hydrolyzed with sodium hydroxide in dimethylformamide-methanol to give a crystalline water-soluble product. However, it was not found possible to prepare an analytically pure sodium salt or the free acid therefrom.

Solubilization of 3,7-diaminodibenzothiophenedioxide (X). To 5 g. (0.02 mole) of 3,7-diaminodibenzothiophenedioxide and 8 g. (0.04 mole) of dimethyl isocyanatoglutarate in a small flask was added 6 ml. of dimethyl sulfoxide. The flask was fitted with a drying tube containing calcium chloride and heated at 70° for 2 hr. The resulting syrup was dissolved in ethanol and treated with 4 g. (0.1 mole) of sodium hydroxide in 6 ml. of water. A taffylike product formed. After warming for 1 hr. at 60° and adding 100 ml. more ethanol, the product became solid. It was ground to a powder under alcohol, collected on a filter, washed with water, and dried; yield, 13 g. This material, which is essentially the tetrasodium salt of 3,7-bis(1,3-dicarboxypropylureylene)dibenzothiophenedioxide is highly soluble in water.

A solution of 3 g. of the sodium salt in water was acidified, warmed, and treated with ethanol until the solid which formed on acidification dissolved. On cooling, the free acid crystallized. Recrystallization from a mixture of ethylacetate and methanol gave a product melting at 175–178° dec.

Anal. Calcd. for $C_{24}H_{24}O_{12}N_4S$: C, 48.6; H, 4.1; N, 9.5; S, 5.4. Found: C, 48.3, 48.6; H, 4.4, 4.7; N, 9.1; S, 5.2.

ROCHESTER 4, N. Y.

[CONTRIBUTION FROM THE GENERAL ELECTRIC RESEARCH LABORATORY]

Preparation of Methyl Esters Containing the 1,3-Dioxane or 2,4,8,10-Tetroxaspiro[5.5]undecane Structure by Ketal Exchange

ROBERT M. LUKES[1]

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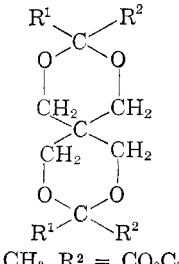
Methyl diesters containing the 2,4,8,10-tetroxaspiro[5.5]undecane structure have been prepared from methyl keto esters and pentaerythritol by ketal exchange between the keto esters and the diacetone ketal of pentaerythritol. The method has been extended to the preparation of methyl hydroxy esters containing the 1,3-dioxane structure by ketal exchange between keto esters and the acetone ketal of 1,1,1-trishydroxymethylethane. Polyesters have been prepared from both types of esters, by transesterification with ethylene glycol in the case of the diesters or self-transesterification in the case of the hydroxy esters.

The coupling of aldehyde esters or keto esters through the nonester carbonyl function provides a route to the preparation of high molecular weight diesters suitable for conversion into linear polyesters by alcohol interchange with glycols. Böeseken and Felix,[2] as part of their intensive study of the structure and reactions of pentaerythritol, prepared a series of just such compounds (I–V) by condensing the appropriate ethyl esters with pentaerythritol.



I. $R^1 = CH_3$, $R^2 = CO_2C_2H_5$
II. $R^1 = CH_3$, $R^2 = CH_2CO_2C_2H_5$
III. $R^1 = CH_3$, $R^2 = CH_2CH_2CO_2C_2H_5$
IV. $R^1 = H$, $R^2 = m\text{-}C_6H_4SO_3H$
V. $R^1 = H$, $R^2 = m\text{-}C_6H_4CO_2H$

The ethyl diester III prepared according to their directions has been found to condense with ethylene glycol under alkaline catalysis to form an insoluble gel, obviously cross-linked.[3]

It was decided to prepare the methyl diester corresponding to III, since past experience had shown that this would be more likely to be a crystalline solid than would the ethyl ester, and hence would be more easily purified. However, to prepare the methyl diester from the crude ethyl diester *via* saponification and re-esterification seemed unnecessarily tedious, and to use the direct condensation of the methyl keto ester with pentaerythritol, distilling the byproduct water as an azeotrope[4] was impractical because of the likelihood of a supervening transesterification and distillation of methanol.

(1) Present address: Locomotive and Car Equipment Dept., General Electric Co., Erie, Pa.

(2) J. Böeseken and B. B. C. Felix, *Ber.*, 61B, 787 (1928).

(3) The cause of the cross linking was no mystery, since III was a liquid purified only by distillation and undoubtedly contained as a contaminant the dihydroxy ester VI, the monoketal of pentaerythritol. This compound was indeed isolated by Böeseken and Felix in their work.

(4) *Cf.* E. J. Salmi, *Ber.*, 71, 1803 (1938); M. S. Newman and R. J. Harper, Jr., *J. Am. Chem. Soc.*, 80, 6350 (1958); R. I. Meltzer *et al.*, *J. Org. Chem.*, 25, 712 (1960).