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On the Preparation of Optically Active Phenyl-*p*-tolylmethanesulphonic Acid and its Racemisation by Sodium Ethoxide

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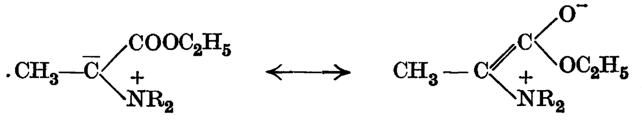
In a series of papers Biilmann and coworkers[1] have investigated the racemisation of optically active propiobetaineesters of the formula:

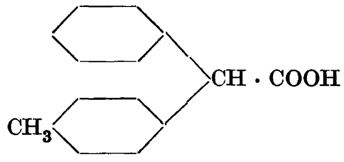
$$\mathrm{CH_3 \cdot CH(\overset{+}{N}R_3) \cdot COOC_2H_5}$$

and related compounds containing sulphur, selenium, phosphorus and arsenic in stead of nitrogen. It was found, that these compounds were racemised immediately by sodium ethoxide and with measurable velocity by different tertiary amines. A plausible explanation of this observation is that a proton may be comparatively easily separated from the asymmetric carbon atom, because of the repelling (acidifying) effect of the positively charged group. The anion formed by this process will be mesomeric to an enolate ion, which is planar, due to the double bond, and accordingly the optical activity will be lost:



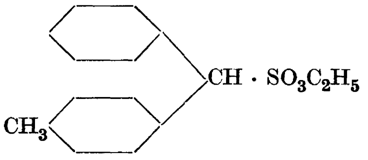
We were interested in investigating an analogous compound containing a sulphonic group in stead of the carboxyl group. In that case no enolization would be expected and accordingly the negative ion would possibly be optically stable.

However, due to difficulties in preparing the desired compounds, we have investigated a compound of a different type: Optically active phenyl-*p*-tolyl-acetic acid (and its esters):



are rapidly racemised too by alkalies, but not by tertiary amines. Ives[2] has shown by experiments with optically active phenyl-*p*-tolyl-deuteroacetic acid that this racemisation proceeds by an ionisation mechanism.

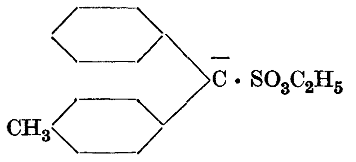
We have therefore studied the racemisation of an ester of the analogous sulphonic acid, phenyl-*p*-tolyl-methanesulphonicacid:



The acid was prepared by the reaction of *p*-methylbenzhydrylbromide with sodium sulphite and resolved through the strychnine salt. The ester was prepared without racemisation by reaction of the silver salt of the sulphonic acid with ethyl iodide.

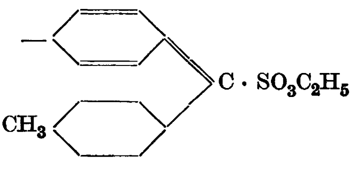
This ester was found to racemise practically immediately by the action of sodium ethoxide, and accordingly it behaved in the same way as the carboxyl derivative.

According to the experiments by Ives this racemisation would be expected to proceed through ionisation by which a negative ion is formed:

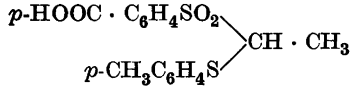


but while the racemisation of the carboxyl derivative may be easily explained by the formation of a planar enolate ion, an analogous explanation is in this case less likely. From the octet theory it was originally concluded that the sulphonyl group does not contain any double bonds and this conclusion was substantiated by several experimental data. However Pauling[3] and Sutton[4] have stated some reasons for accepting the classical formula, but according to Arndt and Eistert[5] their objections to the octet formulas cannot be considered as decisive. Although the validity of the octet theory for sulphur compounds cannot be theoretically deduced, most of the experimental observations point to it as being practically valid in this case.

Other possibilities for explaining our experiments may, however, be considered too: the negative ion might be stabilized by resonance with quinoid forms, which would tend to flatten the ion:



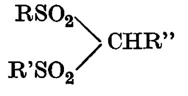
or the negative ion, that is isosteric with an amine, might be instable due to easy inversion, as in the case of amines of the type RR′R″N, which cannot be prepared in optically active forms. Kipping[6] has resolved the compound



$$\left.\begin{matrix} p\text{-HOOC}\cdot C_6H_4SO_2 \\ p\text{-}CH_3C_6H_4S \end{matrix}\right\rangle CH\cdot CH_3$$

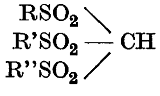
and shown the active form to be easily racemised by alkali. In this case it is not possible to explain the racemisation by the formation of quinoid forms.

We are inclined, therefore, to explain our results as indicating that the negative ion, R_3C^-, is not optically stable in this case, but is easily inverted. The possibility that the sulphonyl group may be enolized cannot, however, be definitely rejected. In this connexion it may be mentioned, that all attempts to resolve compounds of the types:



$$\left.\begin{matrix} RSO_2 \\ R'SO_2 \end{matrix}\right\rangle CHR''$$

and



$$\left.\begin{matrix} RSO_2 \\ R'SO_2 \\ R''SO_2 \end{matrix}\right\rangle CH$$

have failed[7]. In the literature the only indication of the existence of an optically active $RR'R''C^-$ -ion is the result obtained by Wallis and Adams[8], which however we do not consider as conclusive.

EXPERIMENTAL

Sodium *p*-methylbenzhydrylsulphonate

To a solution of 260 g of $Na_2SO_3\cdot 7H_2O$ in 260 ml of water was added 216 g of *p*-methylbenzhydrylbromide and the mixture was refluxed for two hours. On cooling the oily layer becomes very viscous and crystallisation of the sodiumsalt of the sulphonic acid takes place. To avoid this the hot reaction mixture was poured into a preheated separatory funnel and separated rapidly. The water layer was cooled and the sodium salt filtered off, dried, and shaken twice with ether in order to remove the remaining traces of oil. Then the sodium salt was dissolved in 400 ml of absolute ethanol, and a small amount of sodium sulphite removed by filtration. The alcoholic solution was evaporated to dryness and the residue (68 g) recrystallised from water. Yield 59 g ~ 22 %.

$C_{14}H_{13}O_3SNa \cdot 2H_2O$ Calc. Na 7.18 Found Na 7.23

The oily byproduct (105 g) was found to be a mixture of *p*-methylbenzhydrol and di-*p*-methylbenzhydryl ether. By means of constant boiling hydrobromic acid it was easily converted to *p*-methylbenzhydrylbromide, which was used in the next preparation of the sodium salt.

Di-*p*-methylbenzhydryl ether

A sample of the oily byproduct was distilled under reduced pressure. During this treatment the alcohol was converted into the ether and all distilled at 9 mm and 275°. The ether solidified to a colourless, glassy mass that did not crystallise.

$C_{28}H_{26}O$	Calc.	C 88.85	H 6.92
	Found.	» 89.19	» 6.84

p-Methylbenzhydrylsulphonic acid

Twenty g of the sodium salt were dissolved in 40 ml of hot water, and the acid precipitated by means of 100 ml of conc. hydrochloric acid. The acid was filtered off and recrystallised twice from each time 20 ml of water. Yield 12 g ~ 64 %. The acid forms colourless leaves with m. p. 124—125° (dec.).

$C_{14}H_{14}O_3S \cdot 2H_2O$ Calc. Equiv. wt. 290.3 Found Equiv. wt. 299.3

Resolution of the sulphonic acid into optically active components

The cinchonine and brucine salts of the acid crystallised poorly. Recrystallisations of the *l*-menthylammonium salts from water and ethanol and of the *l*-α-phenethylammonium salts from water, ethanol, methanol, chloroform and dioxane did in no case lead to any resolution.

The resolution was effected, however, through the strychnine salts. Strychnine (40.9 g = 0.12 mole) was dissolved in 127 ml of 1 *N* sulfuric acid plus 1 liter of water. The solution was heated to 100° and, under stirring, dropped into a solution of 78 g of sodium *p*-methylbenzhydrylsulphonate (0.24 mole) in 1 liter of water, heated to 80°. The mixture was cooled, and the precipitate (75 g) was filtered off. The mother liquor was heated again to 80°, and 0.12 mole of strychnine sulphate was added dropwise. After cooling 54 g of strychnine salt was filtered off. The first fraction (75 g) was boiled for 1.5 hours with 1800 ml of ethanol, which dissolved only part of the salt. The mixture was cooled and filtered, and the precipitate was reboiled 8 times in the same way, namely with 1450, 1250, 1100 and 5 times 1000 ml of alcohol respectively. At this stage 49.6 g of strychnine salt remained. The second fraction of strychnine salt (54 g) was boiled three times with 900 ml of alcohol each time; 40.6 g remained.

The sulphonic acid was liberated in the following way: 12 g of the strychnine salt from the first crop was shaken in a separatory funnel with 100 ml of 0.2160 *N* barium hydroxide, 600 ml of CO_2-free water and 150 ml of chloroform. By this treatment the chloroform dissolved the strychnine, while the barium salt of the sulphonic acid remained in the aqueous solution. The aqueous layer was extracted twice with 50 ml of chloroform. The chloroform remaining in the aqueous layer was removed by evaporation under reduced pressure. A little excess of 1 *N* sulphuric acid was added, and the mixture was left overnight. The barium sulphate was filtered off and the filtrate concentrated to 50 ml under reduced pressure at 40°. In the same way the acid was liberated from two other 12 g-portions of strychnine salt, and to the combined fractions of sulphonic acid 500 ml of conc. hydrochloric acid were added. The sulphonic acid was filtered off and dried in the air, then it was put in a desiccator and the last trace of hydrogen chloride removed by repeated evacuation; finally it was dried over potassium hydroxide. Yield 16.2 g or 90 % of the theoretical amount. M.p. 115.0°—119.5°. $[\alpha]_D = +7.7°$.

$C_{14}H_{14}O_3S \cdot 2H_2O$ Calc. Equiv. wt. 298.3 Found Equiv. wt. 297.1

The second fraction of strychnine salt yielded the levorotatory acid with $[\alpha]_D = -7.1°$.

Ethyl *p*-methylbenzhydrylsulphonate

Thirteen g of the sulphonic acid were dissolved in 32 5ml of water and 3 % more than the calculated amount of freshly precipitated silver oxide added during two hours under vigorous stirring. The stirring was continued for three hours, the reaction mixture being protected from light. Most of the silver salt was filtered off together with the excess of silver oxide, and the rest of silver salt was isolated from the mother liquor by evaporation to dryness under reduced pressure at a bath temperature of 35°. The silver salt (16 g) was added to a solution of 15 g of ethyl iodide in 110 ml of ether, and the mixture was shaken for 29 hours. Before filtering of the silver iodide 100 ml of benzene was added in order to increase the solubility of the ester. The filtrate was evaporated to dryness under reduced pressure at ordinary temperature. The ester was recrystallised three times from alcohol. Yield 7.8 g $\sim$ 62 %.

$C_{16}H_{18}O_3S$ Calc. S 11.04 Found (Grote-Krekeler) S 10.96

The ester is slightly soluble in ether, cold ethanol and cold methanol, very soluble in benzene and toluene.

Optical rotatory power of the ester ($l = 2$ dm):

Solvent	Concentr. g/10 ml	$t°$	α_D	$[\alpha]_D$
toluene	1	12.50	+ 0.64	+ 3.2
toluene	1	24.98	+ 0.59	+ 2.95
toluene	0.5	24.98	+ 0.30	+ 3.0
benzene	0.5	24.95	+ 0.54	+ 5.4
ethanol	0.12	12.50	+ 0.06	+ 2.5
ethanol	0.12	25.20	+ 0.05	+ 2.1

The *l*-ester and the *d,l*-ester were prepared in the same way. For the *l*-ester in benzene solution was found $[\alpha]_D^{20} = -5.6°$. The melting points of the *l*-ester and the *d,l*-ester are 89.0—89.3° and 65.0—65.5° respectively.

Racemisation of the *d*-ester

Two grams of *d*-ester were dissolved in 166 ml of ethanol, freed from water and carbon dioxide by distillation over magnesium ethoxide and barium oxide successively. Alcoholic sodium ethoxide (the amount equivalent to the amount of ester) was added. The racemisation was very rapid, as stated below, *t* being the time in minutes calculated from the moment of adding the ethoxide:

t :	4	6	10
α :	+ 0.01	0.00	0.00
($l = 2$ dm)			

The uncertainty was 0.01°.

The solution was acidified by means of 0.83 g of glacial acetic acid, concentrated to about 30 ml, diluted by 50 ml of water and extracted twice with 10 ml of benzene. The benzene solution was washed with 5 ml of water and dried over sodium sulfate. The solution showed no optical rotation. By evaporation it yielded 1.73 g of ester, giving a calculated $\alpha = +0.92°$, provided no racemisation had occurred. The regenerated ester had the m.p. 62.0—64.2°. As mentioned above the m.p. of the pure *d,l*-ester is 64.8—65.5°. Mixed m.p.: 62.5—64.9°.

SUMMARY

Phenyl-*p*-tolyl-methanesulfonic acid has been prepared and resolved in optically active components. The ethyl ester of this acid is racemised practically instantaneously by the action of sodium ethoxide. The possible explanations of this racemisation has been discussed.

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