717. *Trans-esterification as a Means of Halide Esterification under Neutral Conditions.*

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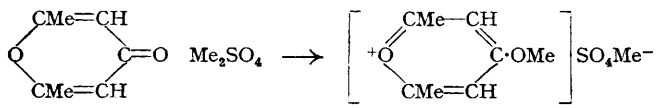
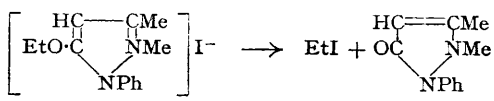
A survey of the value of trans-esterification for conversion of alcohols into halide esters under neutral conditions, with arythiocarbamates as intermediaries, has indicated its inapplicability in presence of more than one ether or acetal grouping.

The problem of esterifying alcoholic groupings in molecular structures, *e.g.*, glycosides, of which other portions are sensitive to acidic conditions, may be attacked by the procedure of double decomposition, but with only slight success. Thus the preparation of iodides from toluene-*p*-sulphonates of glycosides is limited for practical purposes to primary alcoholic groups. Although the method of direct esterification is also clearly inadmissible, the generation of the oxonium condition, on which it depends, can be achieved indirectly in a neutral medium by attack on an unsaturated system to which the oxygen atom is attached; thus, *e.g.*, dimethylpyrone yields 4-methoxy-2 : 6-dimethylpyrylium (methylsulphate) (Kehrmann and Duttendorfer, *Ber.*, 1906, **39**, 1303; Baeyer, *ibid.*, 1910, **43**, 2337) :



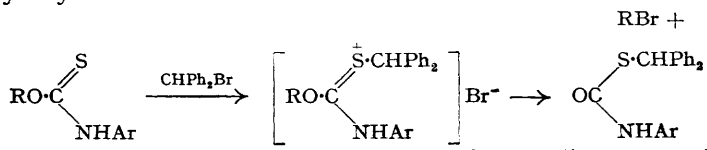
Further, Knorr recorded the thermal decomposition of 5-ethoxy-3-methyl-1-phenylpyrazole methiodide to ethyl iodide and 2 : 3-dimethyl-1-phenylpyrazolone (*Annalen*, 1896, **293**, 5, 13) :



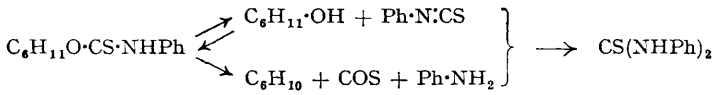
Similar relations between α- or γ-alkoxy- or -thioalkyl derivatives in the pyridine and quinoline series and corresponding *N*-methyl-pyridones or -quinolones are familiar.

These reactions illustrate the feasibility in principle of using the ester of one alcohol to esterify another irreversibly through the intermediary of a suitable unsaturated system, and we apply to such a process the term "conjugate trans-esterification," to distinguish it from the equilibration of carboxylic esters, usually connoted by "trans-esterification." The practical need of a simple preparation of the unsaturated system from the alcohol led us to select the *O*-alkyl thiocarbanilates, which are readily available from sodium alkoxides and phenyl *iso*thiocyanate (Bistryzcki, *Helv. Chim. Acta*, 1919, **2**, 131). Wheeler and Barnes (*Amer. Chem. J.*, 1900, **24**, 60) demonstrated the "conversion" of the *O*-ethyl and -*iso*butyl thiocarbanilates into their *S*-isomerides when heated with the corresponding iodide, and in other papers (*ibid.*, 1899, **22**, 141; 1900, **24**, 189, 424) analogous transformations in related types of compounds were recorded. Those authors also realised that the reactions depended on preliminary formation of a sulphonium halide. Later, Biilmann (*Annalen*, 1909, **364**, 319) recorded similar reactions in the xanthate series and found diphenylmethyl bromide to be a very effective agent in promoting, *e.g.*, the formation of ethyl bromide from *O*-ethyl *S*-carboxymethyl dithiocarbonate.

We have now found that simple *O*-alkyl phenyl- and α-naphthyl-thiocarbamates react with diphenylmethyl bromide readily in benzene, with extensive formation of *S*-diphenylmethyl arylthiocarbamates :



But, since isolation of the bromide formed was impeded by co-distillation with the solvent, it was preferable to effect the reaction at 100—120° under reduced pressure in absence of solvent. A complication arises from the tendency of thiocarbanilates to suffer reversible thermal decomposition (Hofmann, *Ber.*, 1869, **2**, 120; 1870, **3**, 172). Thus the ethyl derivative furnishes alcohol and phenyl *iso*thiocyanate: $NHPh{\cdot}CS{\cdot}OEt \rightleftharpoons EtOH + Ph{\cdot}N{:}CS$. In some instances *s*-diphenylthiourea is also formed, owing in the first place to a variant of the Tschugaeff decomposition of methyl xanthates, followed by combination of the aniline so formed with phenyl *iso*thiocyanate from the decomposition just mentioned. Thus we have found thermal decomposition of *cyclo*hexyl thiocarbanilate to yield, besides *cyclo*hexanol and diphenylthiourea, *cyclo*hexene and carbon oxysulphide :



Thiocarbamates derived from *sec.*-octyl alcohol, 2-methoxyethanol, and 1 : 3-dimethoxypropan-2-ol and, less markedly as regards diphenylthiourea formation, from 1 : 3-*O*-benzylideneglycerol behaved similarly. On the other hand, the molecular configurations of corresponding derivatives of 1 : 2-*O-iso*propylideneglycerol and of di-*O-iso*propylideneglucose, -galactose, and -mannose are unfavourable to occurrence of a Tschugaeff reaction (cf. Cram, *J. Amer. Chem. Soc.*, 1949, **71**, 3883), so that they suffered only the reversible dissociation.

The thermal effect of reaction with diphenylmethyl bromide or chloride determines the occurrence, to some extent, of the above reactions in our preparation of bromides or chlorides from the thiocarbamates. This will be apparent from the comparison of crude yields in Tables 1 and 2 with those of pure material resulting from distillation of crude product over mercuric oxide.

TABLE 1. *Reaction of thiocarbamates with diphenylmethyl bromide.*

Thiocarbamate	Bromide, % Crude	Pure	n_D	B.p./mm.	Br, % Found	Calc.
2-Methoxyethyl thiocarbanilate ...	111	90	1·4500	111·5°/771	57·7	57·5
2-Methoxy-1-methoxymethylethyl thiocarbanilate	86·5	70·5	1·4560	174·5°/763	43·7	43·8
*cyclo*Hexyl thiocarbanilate	72·5	37·8 *	1·4965	160°/751	49·3	49·1
sec.-Octyl α-naphthylthiocarbamate	75	61·5	1·4500	80·5°/27	41·1	41·4
1 : 2-*O-iso*Propylideneglycerol thiocarbanilate	—	21·5	1·4738	178°/756	40·7	41·0
Cholesteryl thiocarbanilate	—	47	—	(M. p. 97—98°)	—	—

* *cyclo*Hexene equivalent to 31·8% of the bromide was isolated.

TABLE 2. *Reaction of thiocarbamates with diphenylmethyl chloride.*

Thiocarbamate	Chloride, % Crude	Pure	n_D	B. p./mm.	Cl, % Found	Calc.
2-Methoxyethyl thiocarbanilate ...	85·1	75·2	1·4105	88·3°/750	37·4	37·8
2-Methoxy-1-methoxymethylethyl thiocarbanilate	92·3	57·5	1·4350	156°/750	25·1	25·6
sec.-Octyl α-naphthylthiocarbamate	—	46·5	1·4248	171°/765	23·8	23·9
1 : 2-*O-iso*Propylideneglycerol thiocarbanilate	—	6	1·4370	159°/759	23·5	23·6

Acetone was one of the products obtained by treating the thiocarbanilate of 1 : 2-*O-iso*propylideneglycerol with diphenylmethyl bromide, presumably owing to the action of

hydrogen bromide generated by some decomposition of diphenylmethyl bromide. This limits the temperature applicable to the use of the bromide with less reactive thiocarbamates, *e.g.*, of di-*O*-*iso*propylidene-glucose, -mannose, and -galactose, 1 : 3-*O*-benzylideneglycerol, and methyl 2 : 3 : 6-tri-*O*-methylglucoside, and accounts for the blackening which ensues from attempts to enforce reaction. Diphenylmethyl chloride does not suffer from this defect but is also otherwise less reactive.

(+)-*sec.*-Octyl alcohol was converted through its α-naphthylthiocarbamate into the (−)-bromide, of which the rotatory power was sensibly higher than that previously recorded, presumably because the conditions of its preparation reduced to a minimum the opportunity of racemisation by bromide ions (cf. Bergmann and Polanyi, *Naturwiss.*, 1933, **21**, 378). This result confirms the expectation that an S_N2 mechanism is involved in the above instances, and it is thus the more striking, though in accord with other expectations (cf. Barton, *J.*, 1953, 1027), that cholesterol is converted by our procedure into cholesteryl bromide without inversion of configuration.

The yield of bromide from 1 : 2-*O*-*iso*propylideneglycerol by the present method, though superior to that achieved through the toluene-*p*-sulphonate (English and Schuller, *J. Amer. Chem. Soc.*, 1952, **74**, 1361), is nevertheless very moderate. This may be due to the alternative site of attack for diphenylmethyl bromide offered by the oxygen atoms of the acetal grouping for, when the proportion of such alternatives is increased, as in 1 : 2-3 : 4-di-*O*-*iso*propylidenegalactose, 2 : 3-5 : 6-di-*O*-*iso*propylidenemannose, and 1 : 2-5 : 6-di-*O*-*iso*propylideneglucose, the method fails. As would then be expected, it is also inapplicable to the dibenzyl mercaptal of 2 : 3-5 : 6-di-*O*-*iso*propylideneglucose.

Experimental

Characteristic Data of Thiocarbamates.—These are given in Tables 3 and 4.

Table 3. *Phenylthiocarbamates (thiocarbanilates).*

Alcohol	M. p.	Yield, %	Formula	Found, % C	H	N	S	Required, % C	H	N	S	$[\alpha]_D^{20}$
*cyclo*Hexanol	79—80°	57	$C_{13}H_{17}ONS$	66·7	7·4	6·0	—	66·4	7·3	5·7	—	—
2-Methoxyethanol	45—46	71	$C_{10}H_{13}O_2NS$	56·8	5·7	6·7	15·6	56·9	6·2	6·6	15·1	—
1 : 3-Dimethoxypropan-2-ol	39—40	57	$C_{12}H_{17}O_3NS$	56·2	6·8	5·4	12·6	56·6	6·7	5·5	12·5	—
1 : 3-*O*-Benzylideneglycerol	158—159	—	$C_{17}H_{17}O_3NS$	65·2	5·5	4·2	9·6	64·8	5·4	4·5	10·1	—
	136—138	—	—	65·2	5·1	4·7	—					
1 : 2-*O*-*iso*Propylideneglycerol	58·5—59·5	81	$C_{13}H_{17}O_3N$	58·6	6·4	5·4	—	58·5	6·4	5·3	—	—
1 : 2-5 : 6-Di-*O*-*iso*propylidene-D-glucose	Amorphous	97	$C_{19}H_{25}O_6NS$	57·8	6·4	3·8	8·4	57·8	6·4	3·5	8·1	−49·7° ($CHCl_3$)
1 : 2-3 : 4-Di-*O*-*iso*propylidene-D-galactose	135·5—136·5	80		58·0	6·4	3·7	8·1					−76·6 ($CHCl_3$)
2 : 3-5 : 6-Di-*O*-*iso*propylidene-D-mannose	114·5—116	65	—	57·8	6·6	3·6	—					+14·8 ($CHCl_3$)
Cholesterol	179—180	44	$C_{34}H_{51}ONS$	78·8	9·9	2·9	6·3	78·5	9·9	2·7	6·1	−5·2 ($CHCl_3$)

Table 4. *α-Naphthylthiocarbamates.*

Alcohol	M. p.	Yield, %	Formula	Found, % C	H	N	Required, % C	H	N	$[\alpha]_D^{20}$
*cyclo*Hexanol	109—110°	68	$C_{17}H_{19}O_2NS$	71·5	7·1	5·0	71·6	6·7	4·9	—
sec.-Octyl alcohol	47·5—49	59	$C_{19}H_{25}ONS$	72·8	7·8	4·5	72·5	8·0	4·5	+16° (EtOH)
(+)-*sec.*-Octyl alcohol	Syrup	47				4·5				
1 : 2-5 : 6-Di-*O*-*iso*propylidene-D-glucose	Syrup	40	$C_{23}H_{27}O_6NS$	61·8	6·1	3·4	62·1	6·1	3·2	−49·3 ($CHCl_3$)
Methyl 2 : 3 : 6-trimethyl-D-glucoside	131·5—132·5	—	$C_{21}H_{27}O_6NS$	60·3	6·5	3·4	60·0	6·5	3·3	+78·6 (Me_2CO)
2 : 3-5 : 6-Di-*O*-*iso*propylidene-D-glucose dibenzylmercaptal	Syrup	69	$C_{37}H_{41}O_5NS_3$	65·9	6·0	2·1	65·8	6·1	2·1	−38·5 (C_6H_6)

Thermal Decomposition of Thiocarbamates.—*cyclo*Hexyl thiocarbanilate distils unchanged under 0·2 mm. pressure, but in an atmosphere of nitrogen at 220—240° (bath-temp.)/760 mm. it (2·808 g.) furnished a distillate from which were separated *s*-diphenylthiourea (0·297 g.), m. p. and mixed m. p. 148—149°, and fractions (*a*), a very volatile liquid (0·275 g.), b. p. 60—90°, and (*b*), *cyclo*hexanol (0·588 g.), b. p. 161—164°, n_D^{21} 1·5092 (thiocarbanilate, m. p. and mixed m. p. 77—78°). The distillate condensed by liquid air contained carbon oxysulphide, identified by sodium nitroprusside coloration after absorption in alkali, and *cyclo*hexene (0·265 g.), b. p. 80—83°, n_D^{21} 1·4508; ψ-nitrosite, m. p. 143—144° (Wieland and Blumich, *Annalen*, 1921, **424**, 86, 88, quote m. p. 145°).

Similar results were obtained from experiments with *cyclo*hexyl α-naphthylthiocarbamate and, under reduced pressure, with *sec.*-octyl α-naphthylthiocarbamate and the thiocarbanilates of 2-methoxyethanol, 1 : 3-dimethoxypropan-2-ol, and 1 : 2-*O*-*iso*propylideneglycerol.

Thermal decomposition of 1 : 2-3 : 4-di-*O*-*iso*propylidenegalactose thiocarbanilate (3·483 g.) under 15 mm. pressure of nitrogen at 220° (bath-temp.) yielded a distillate from which were separated (*a*) phenyl *iso*thiocyanate (0·989 g.), b. p. 130° (bath-temp.)/19 mm., n_D^{23} 1·6445, characterised as *s*-diphenylthiourea, m. p. and mixed m. p. 154—155°, and (*b*) di-*O*-*iso*propylidene galactose (1·785 g.), b. p. 140° (bath-temp.)/0·03 mm., n_D^{23} 1·4672, $[\alpha]_D^{20}$ −59·6° (*c*, 1·74 in $CHCl_3$) (acetate, m. p. 108—109°). No carbon oxysulphide could be detected by absorption in alkali. The thiocarbanilates of 1 : 3-dimethoxypropan-2-ol, 1 : 3-*O*-benzylideneglycerol (both modifications), 1 : 2-5 : 6-di-*O*-*iso*propylideneglucose, and 2 : 3-5 : 6-di-*O*-*iso*propylidenemannose yielded similar results.

Treatment of Thiocarbamates with Diphenylmethyl Bromide.—The distillate obtained by heating a mixture of the thiocarbamate with 1 mol. of the bromide at 120—130°/15 mm. was collected in a receiver cooled by liquid air and redistilled over mercuric oxide or potassium permanganate to remove sulphur-containing impurities. The residue from the first distillation was *S*-diphenylmethyl thiocarbanilate or *α-naphthylthiocarbamate*; after recrystallisation from alcohol, these had, respectively, m. p. 138—139·5° (Becker and Bistryzcki, *loc. cit.*, quote m. p. 135—136°) (Found: N, 4·5; S, 9·5. Calc. for $C_{20}H_{17}ONS$: N, 4·4; S, 10·0%), and m. p. 162—163° (Found: C, 77·6; H, 5·4; N, 4·1; S, 8·8. $C_{24}H_{19}ONS$ requires C, 78·0; H, 5·2; N, 3·8; S, 8·7%).

Cholesteryl bromide was isolated (after fusion of a mixture of the thiocarbanilate with the bromide for 1 hr. at 120°) by recrystallisation from alcohol.

The respective yields and physical and analytical data are summarised in Table 1. The crude *cyclo*hexyl bromide contained *cyclo*hexene, b. p. 83°, n_D^{22} 1·44501, and carbon oxysulphide was detected in the gaseous distillate.

Non-reactivity with the bromide of thiocarbamates already cited was shown by observation of the rotatory power of the reactant mixture in benzene where this was not inhibited by darkening, or by recovery in good yield of the unchanged material from solution or mixture after fusion at 120°.

Treatment of Thiocarbamates with Diphenylmethyl Chloride.—A similar procedure with diphenylmethyl chloride afforded the products whose relevant physical and analytical data are shown in Table 2.

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