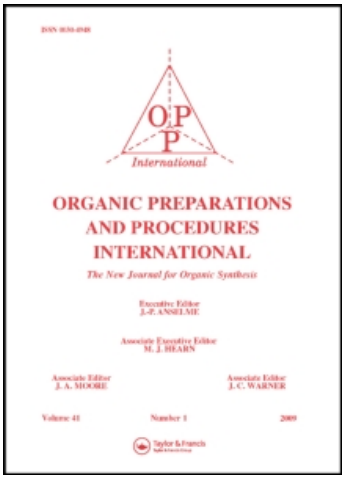

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N-SUBSTITUTION OF SACCHARIN UNDER PHASE-TRANSFER CONDITIONS

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OPPI BRIEFS

N-SUBSTITUTION OF SACCHARIN UNDER PHASE-TRANSFER CONDITIONS

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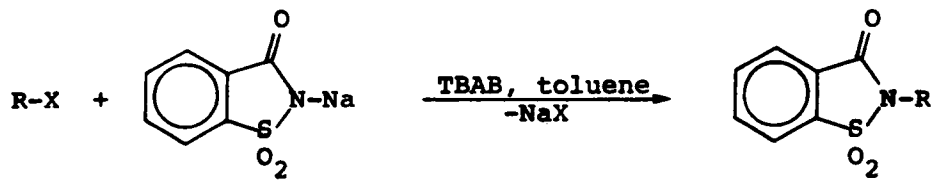
Phase-transfer catalysis has been successfully applied to the alkylation of NH groups in which the acidity is enhanced by neighboring electron-withdrawing substituents as in amides, lactams, imides and sulfonamides.[1-4] The present paper reports that the phase transfer-catalysis was also successful in preparing N-alkyl(IV) and N-acyl(V) derivatives of saccharin. These preparations were carried out via the reaction of sodium saccharin(II) with alkyl and acyl halides(I) in toluene in the presence of catalytic amounts of tetrabutylammonium bromide (TBAB) III) under phase-transfer conditions. Several methods have been



I III a) R = Alkyl b) R = Acyl IV or V

used to prepare IV[5-12] and V.[13-15] Indeed, small amounts of saccharin occurring in biological samples have been methylated by the extractive alkylation procedure using tetrabutylammonium hydrogen sulphate and methyl iodide, to obtain samples for analytical studies.[16]

We found that the reaction did not take place when the catalyst was not present even when the very reactive benzyl bromide or benzoyl chloride were employed. It was determined that the secondary halide cyclohexyl bromide, undergoes elimination and that the alkyl halide reactivities decrease in going from bromide to chloride and also by increasing the length of the alkyl chain. This loss in reactivity was balanced in part by a longer period of heating and/or raising either the temperature or the ratio of catalyst. It was demonstrated that the substitution first takes place on the carbonyl oxygen atom producing and O-alkylsaccharin (kinetic product) which slowly isomerizes to the corresponding N-alkyl derivative (thermodynamic product) by increasing the time of heating. The isomerization was drastically accelerated by raising the temperature. A typical example of this was the synthesis of N-butylsaccharin (Table). When the reaction was carried out at 85^{o} and stopped after 8 hrs, O-butyl saccharin was isolated in 60% yield; IR analysis indicated the loss of C=O absorption. Nonetheless, when the reaction was allowed to proceed for 24 hrs, N-butylsaccharin was formed almost exclusively, with strong absorption at 1730 cm^{-1} due to C=O group. On the other hand, isolated and purified O-butylsaccharin was dissolved in toluene with the catalyst; when this solution was heated at 100^{o} for 10 hrs, it yielded N-butylsaccharin quantitatively. This transformation did not take place when there was no ammonium salt. Adequate control of both time and temperature of reaction thus permits obtention of an O-alkyl or an N-alkylsaccharin.

EXPERIMENTAL

IR spectra were obtained as KBr disks on a Beckman IR-8 spectrophotometer. ^{1}H-NMR spectra were obtained in deuterated chloroform using a Varian T-60 spectrometer with TMS as internal standard. Mass spectra were measured on a Finnigan 3300 F-100 instrument. Elemental analysis were carried out in an F & M Analyzer 185.

General Procedure.- A suspension of dry powdered sodium saccharin (0.49 g, 2.4 mmol) in toluene (10 ml), the alkyl (or acyl) halide (2 mmol) and the tetrabutylammonium bromide (0.06 g, 0.24 mmol) were placed in a flask equipped with a reflux condenser and a magnetic stirrer and heated to the appropriate temperature in a bath with stirring. The course of the reaction was monitored by thin-layer chromatography and the spots visualized with iodine. When the reaction was complete (consumption of the halide), the cooled reaction mixture was filtered and the precipitate washed with toluene. The combined organic phase was evaporated under vacuum and the solid obtained chromatographed on silica gel (8 g) with chloroform as eluent. Evaporation of the solvent afforded the N-derivatives which were recrystallized when necessary. For N-benzoyl and N-acetyl derivatives, the reaction mixture had to be filtered while hot, the solvent evaporated and the product recrystallized from absolute ethanol. The structures of the derivatives were confirmed by spectroscopic means.

N-isoamylsaccharin.

Anal. Calcd. for $C_{12}H_{15}NO_3S$: C, 56.90; H, 5.96; N, 5.52

Found: C, 57.23; H, 6.10; N, 5.79

IR (neat): 2950, 2923, 2870, 2845, 1730, 1330, 1180, 1388, 1370 cm^{-1}. ^{1}H-NMR ($CDCl_3$/TMS): δ 7.75 (s, 4 ArH); 3.71 (t, 2H, J = 7 Hz); 7.70 (m, 3H); 0.95 (d, 6 H, J = 5 Hz).

TABLE

N-Alkylation and N-Acylation of Sodium Saccharin Under Phase-Transfer Catalytic Conditions[a]

Reactant I	Reaction conditions temp. (°C)[b]/ time (hrs)	Yield (%)[c] IV	V	n_D^{20} or mp. (°C)[d] (solvent)	Ref.
n-C_4H_9Br	85/20	90	-	38-39.5 (pet. ether)	5,6
i-$C_5H_{11}Br$	85/20	90	-	n_D^{20} 1.5294 syrup	-
n-$C_6H_{13}Br$	85/30	80	-	n_D^{20} 1.5291 syrup	17,18
n-$C_8H_{17}Br$	85/40	85	-	n_D^{20} 1.5224 syrup	17,18
n-$C_{12}H_{25}Br$	100/56	85[e]	-	47-48 (ethanol-water)	6
n-$C_{18}H_{37}Br$	105/72	80[e]	-	70-71 (pet. ether)	6,7
 -Br	90/72	0[e,f]	-		-
CH_2=$CHCH_2Br$	60/6	91	-	89-90	5
$PhCH_2Br$	80/6	91	-	109-110	6
	80/10	0[g]	-		-
$PhCH_2Cl$	80/6	10	-		-
PhCOCl	80/0.75	--	88	162-165 (abs. ethanol)	14
	80/0.75	--	0[g]		-
CH_3COCl	30/0.75	--	85	190-192 (abs. ethanol)	14,15
$CH_3(CH_2)_{12}COCl$	80/3	--	90	91-92	13,14

a) The molar ratio reactant/sodium saccharin/catalyst was 1/1.2/0.12. b) Bath temperature. c) Yields of isolated products based on I. d) Melting points are uncorrected. e) Twofold amount of catalyst was used. f) Cyclohexene was produced exclusively. g) Catalyst was not added.

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