Synthesis of Pure Secondary Alkyl Bromides

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A satisfactory preparative reaction for the conversion of secondary alcohols to alkyl bromides without rearrangement is described. The reaction consists of esterification of the alcohol with tosyl chloride followed by treatment of the ester with a concentrated solution of inorganic bromide in DMF. Kinetic and infrared data support the claim for no rearrangement.

THE SYNTHESIS of compounds of pharmaceutical interest frequently calls for the conversion of alcohols to halides to be used as intermediates. It has been long recognized, but frequently ignored, that conventional reagents (PBr_3, HBr) for this transformation often lead to mixtures of bromides, especially in the case of secondary alcohols (1). Such rearrangement is obviously undesirable in pharmaceutical syntheses.

In so far as it is generally accepted that the rearrangement is due to a carbonium ion intermediate in an S_N1 displacement in the conventional reaction, it was logical to devise a reaction obviating this step. Thus, Pines *et al.* synthesized isomer-free pentyl bromides from 1-pentanol, 2-pentanol, and 3-pentanol by treating their tosylates with a suspension of sodium bromide in diethylene glycol for long reaction times (1). Unfortunately, this reaction was not satisfactory for routine laboratory use due to low yields.

Many inorganic bromides are relatively soluble in dimethylformamide; it has been reported that dehydrohalogenation is facile in DMF solutions of a variety of metal chlorides (2).

A later report using a homogeneous system of tosylate and calcium bromide in DMF gave high yields (about 60% over-all) of substituted cyclopentyl bromides (3). However, in the latter report it was not unequivocally established that rearrangement did not occur. It was therefore germane to determine if the preparative scale synthesis using bromide–DMF did not display rearrangement.

EXPERIMENTAL

Preparation of Tosylates.—Commercially available[1] samples of 1-pentanol, 2-pentanol, and 3-pentanol were esterified with tosyl chloride according to the procedure of Streitweiser, as modified in an earlier report (3). For purposes of kinetic determinations, 1-pentyl tosylate was purified by distillation at reduced pressure.

Preparation of Bromide–DMF Reagents.—Samples of $CaBr_2$ and LiBr were dried to constant weight at 155° (5 days). Approximately saturated solutions were prepared of (*a*) LiBr in DMF, (*b*) LiBr in DMF containing 1% water, (*c*) LiBr in DMF containing 3% water, and (*d*) $CaBr_2$ in DMF. Approximate concentrations attained were (*a*) 1 *M*, (*b*) 1.25 *M*, (*c*) 2.0 *M*, and (*d*) 0.45 *M*, respectively. Each was standardized by titration with silver nitrate to dichlorofluorescein end point.

Kinetics Studies.—The reaction vessel was a 50-ml. Morton flask equipped with a parenteral vial stopper and mounted in a constant-temperature bath maintained at 30.0° ± 0.08°. Quantities of bromide–DMF solution and tosylate were mixed to permit initial ratios of Br^-–tosylate of 2:1. Periodically, 0.5-ml. samples were removed, quenched, and assayed for bromide ion as previously described (3). (In some determinations, especially with crude tosylates in preparative runs, it was observed that eosin is a superior indicator to dichlorofluorescein.) Second-order rate constants were calculated from these data. These values were determined for the reaction of 1-pentyl tosylate with the four bromide–DMF reagents described above.

Preparative Scale Rearrangement Studies.—The infrared spectra[2] were obtained of samples of 1-bromopentane, 2-bromopentane, and 3-bromopentane prepared by preparative scale (0.25 mole of alcohol) reactions using the dry LiBr–DMF reagent according to the previously reported procedure (3). Yields and boiling points were, respectively: 59%, 128–130°; 58%, 116–118°; and 68%, 118–120°. [Reported b.p. 129.7°, 117.2°, and 119.2°, respectively (1).]

The infrared spectrum was also obtained from a sample of "2-bromopentane" prepared by treating 2-pentanol with aqueous HBr according to an established procedure (1), b.p. 115–118°. [Reported (1) b.p. 115–117.°]

RESULTS AND DISCUSSION

The displacement reaction between tosylate and bromide in DMF followed second-order kinetics, as would be expected; this *suggests* that the reaction does proceed by a path not involving a carbonium ion. The rate constants for the reaction of 1-pentyl tosylate with DMF solutions of dry LiBr, LiBr with 1% water, and LiBr with 3% water were 8.95×10^{-4}, 6.81×10^{-4}, and 5.31×10^{-4} L./mole-sec., respectively. The rate constant with dry $CaBr_2$ in DMF was 5.83×10^{-4} L./mole-sec. While it has been customary to allow the displacement reaction to continue for 6–10 hr., these experiments also indicated that the reaction is essentially complete in approximately 3–5 hr. Rarely is more than 60% of the theoretical amount of bromide ion removed from the mixture, although the significance of retarded bromide uptake in long reactions of this type is clouded by the fact that alkyl bromides slowly interact with DMF (4). Water does not alter the course of the reaction significantly, and the presence of 3% water permits the reaction volume to be halved.

The infrared spectra produced by the 1-, 2-, and 3-bromopentanes *via* tosylate displacement were

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[2] Perkin-Elmer Infracord, model 137.

superimposable on those published (in the 7–15 μ range) for structural-isomer-free pentyl halides (1). Furthermore, the spectrum of 2-bromopentane was not superimposable on any of the three pure samples, but was qualitatively identical to a deliberate mixture of pure 2- and 3-bromopentane.

It is apparent that the conversion of secondary alcohols not sterically hindered toward S_N2 displacements to bromides may be carried out by this reasonably simple procedure without rearrangement.

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Synthesis and Pharmacological Investigations of Certain Trimethoxycinnamamides

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Three new *N,N*-disubstituted 3,4,5-trimethoxycinnamamides have been prepared, and these, as well as some other previously described compounds of this class, have been evaluated for possible pharmacological action. No significant cardiovascular, somatic, visceral, or central nervous system effects were noted.

THE REPORT of the tranquilizing action of *N,N*-disubstituted trimethoxybenzamides (1) was correlated with the observation that a number of biologically active compounds occurring in nature contain the trimethoxyphenyl, trimethoxybenzoyl, or trimethoxycinnamoyl groups as a part of their structure (*e.g.*, the alkaloids of rauwolfia, colchicine, and mescaline). Indeed, the new alkaloid from *Piper longum*, piplartine, has been identified as the piperidide of 3,4,5-trimethoxycinnamic acid (2).

As the similarity in physical properties and chemical reactivity of a compound and its vinylog is well known (3), it would appear that this correlation might be extended to include physiological action. Indeed, continued investigation into the pharmacology of vinylogous substances appears to be warranted on the basis of interesting pharmacological effects elicited by vinylogs of well-known medicinal agents (4–9).

In view of the above, it appeared to be of interest to study the pharmacological action of certain trimethoxycinnamamides; during the course of this work, other workers reported five of the compounds prepared in this project (10, 11). The results of these are given in this paper along with the results obtained with similar compounds which had not previously been reported. In fact, interest was heightened by the report of others (11) to the effect that the morpholide of 3,4,5-trimethoxycinnamic acid was more active than meprobamate in reducing spontaneous mobility and in prolonging barbiturate hypnosis in mice.

These reports led to the preparation of additional 3,4,5-trimethoxycinnamamides for pharmacological evaluation; these new compounds involved the tetrahydroharmane moiety, a bicyclic amide and an anilide. The tetrahydroharmane moiety appears in the structure of the alkaloids of rauwolfia; the bicyclic amides have become of interest as analgesic agents (12), and anilides are well known as potential analgesics.

EXPERIMENTAL

The preparative procedure followed was patterned after that of Vargha and his associates (1) and Cerbai and his co-workers (11), *i.e.*, the acid chloride was treated with the appropriate amine. The compounds along with pertinent data are listed in Table I.

PHARMACOLOGICAL DATA

Although these compounds were reported by others during the course of this work, compounds I–V were evaluated for biological activity in order to obtain comparative data for the studies with compounds VI–VIII. The cinnamamides, I–IV and VI, demonstrated no significant cardiovascular, somatic, or visceral effects in an initial pharmacological profile when administered over a wide dosage range (50–2000 mg./Kg.) to anesthetized dogs; compound V demonstrated slight hypotensive and positive chromotropic effects, and compound VIII exhibited a slight hypotensive effect. Compound VII elicited a nongraded hypotensive effect coupled with fleeting intestinal relaxant effects. Compounds I–IV displayed weak central nervous system depressant effects when administered over a dosage range of 50–2000 mg./Kg.; compound VI demonstrated the same effects only at a moderately high dosage level, and compounds VII and VIII were inactive.

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