

REARRANGEMENT STUDIES WITH C¹⁴IV. THE ABSENCE OF REARRANGEMENT IN THE SCHMIDT REACTION WITH 3-PHENYLPROPIONIC ACID-2-C¹⁴*

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The Schmidt reaction is usually considered to include the transformation of carboxylic acids to amines and of ketones to amides by the action of hydrazoic acid and a strong mineral acid catalyst such as sulphuric acid. The mechanism of the reaction with RCOOH is generally depicted as involving a migration of R, with an unshared electron-pair, to an electron-deficient nitrogen after a union or co-ordination between the carbon atom of the carboxyl and a nitrogen atom of hydrazoic acid (2, 13). No rearrangement in the R group would be expected since the R group migrates with complete retention of configuration as observed in the similar Hofmann, Lossen, and Curtius reactions (2). However, in 1949, Schuerch and Huntress (11) assumed the formation and rearrangement of an intermediate carbonium ion to account for the products obtained in the Schmidt reaction with triethylacetic acid. The degradation of C¹⁴-labeled carboxylic acids by the Schmidt reaction has been employed in both biochemical (6, 12) and mechanistic (9) studies, and if the degradation of labeled RCOOH should proceed through an intermediate R⁺ ion, isotope position rearrangement in the R group would invalidate conclusions drawn from such degradative data.

Recently, Phares and Long (8) have demonstrated the feasibility of degrading C¹⁴-labeled succinic acid by the Schmidt reaction. However, in this case, it is not possible to tell whether any isotope position rearrangement has taken place in the symmetrical product, ethylenediamine. Phares has also reported the Schmidt degradation of acetic and propionic acids labeled with C¹⁴ in various positions (7). Although the activity in practically all the unlabeled fragments was negligibly low as expected, the degradation of propionic acid-3-C¹⁴ showed an average of 1.5% of the total activity in the C-2 position. Phares attributed this to contamination. On the other hand, if one were to assume that the ethyl cation is an intermediate in the Schmidt reaction with propionic acid-3-C¹⁴, the activity found in the C-2 position may be conceived as arising from a 1,2-hydride shift in the ethyl cation. Isotope position rearrangement of this order of magnitude in the ethyl cationic system has actually been observed by Roberts and Yancey (10). These workers have found that, in the reaction of ethylamine-1-C¹⁴ with nitrous acid, the resulting labeled ethyl alcohol contained 1.5% of the rearranged product, ethyl-2-C¹⁴ alcohol.

In view of the above considerations, it was thought to be worth while to investigate whether isotope position rearrangement would take place in a Schmidt reaction with an acid which would be expected to give rise to a considerable degree of rearrangement if the reaction were to proceed through a carbonium ion intermediate. The Schmidt reaction with 3-phenylpropionic acid-2-C¹⁴ (hydrocinnamic acid-2-C¹⁴) was, therefore,

* For Paper III, see Reference 3.

carried out. Should the reaction proceed through an R^+ intermediate, isotope position rearrangement in the phenylethyl cationic system would be expected since rearrangements of up to 50%, or complete equilibration, of the C^{14} -labeled atoms from the C-1 to the C-2 positions in the phenylethyl system have been observed in several reactions where the phenylethyl cation was likely involved (3, 4, 5).

3-Phenylpropionic acid-2- C^{14} , or hydrocinnamic acid-2- C^{14} , was prepared from treatment of 2-phenylethyl-1- C^{14} -magnesium chloride with carbon dioxide as previously described (5).

A chloroform solution of 3.5 g. of 3-phenylpropionic acid-2- C^{14} was placed in a three-necked round-bottomed flask fitted with reflux condenser, dropping funnel, thermometer, and magnetic stirrer. An excess of hydrazoic acid in chloroform solution, prepared as described by Wolff (13), was introduced. Concentrated sulphuric acid (12 ml.) was then added dropwise with constant stirring. The reaction vessel was immersed in a water bath maintained at 40–45° C. Additional hydrazoic acid solution was occasionally added to ensure complete reaction. After it had been stirred for 2 hours, the resulting mixture was poured into ice water, and the aqueous layer separated. The organic layer was further extracted with water and the combined aqueous extracts made basic with 50% sodium hydroxide solution. The product was steam distilled into dilute hydrochloric acid. After the distillate had been evaporated to dryness, the residue was recrystallized from absolute ethanol to yield 2.4 g. (65%) of 2-phenylethylamine hydrochloride, m.p. 217° C., lit., m.p. 217° C. (1).

Part of the 2-phenylethylamine hydrochloride was converted to benzoic acid by alkaline potassium permanganate oxidation (4).

All compounds were assayed for radioactivity, the results being listed below.

	3-Phenylpropionic acid-2- C^{14}	2-Phenylethylamine hydrochloride	Benzoic acid	
			Run I	Run II
Corrected activity* (c.p.m. on a molar basis)	13,869±93	13,336±84	4±7	7±7

*All compounds were converted to barium carbonate and counted as infinitely thick samples of constant geometry in a gas flow Geiger counter. Correction for dilution by non-labeled carbon atoms was made by multiplying the observed activity by the number of carbon atoms per molecule in the compound counted.

The fact that the benzoic acid derived from the oxidation of 2-phenylethylamine hydrochloride obtained in the Schmidt reaction with 3-phenylpropionic acid-2- C^{14} contained no radioactivity clearly indicates that there is no isotope position rearrangement. The phenylethyl cation is, therefore, not involved in this reaction. Thus it would appear quite reasonable to conclude that, with the probable exception of such special cases as triethylacetic acid, the Schmidt reaction with $RCOOH$, in general, does not involve R^+ ion as an intermediate. One may, therefore, utilize this reaction for degradation of labeled compounds without undue suspicion that isotope position rearrangements might occur during the process of the degradation.

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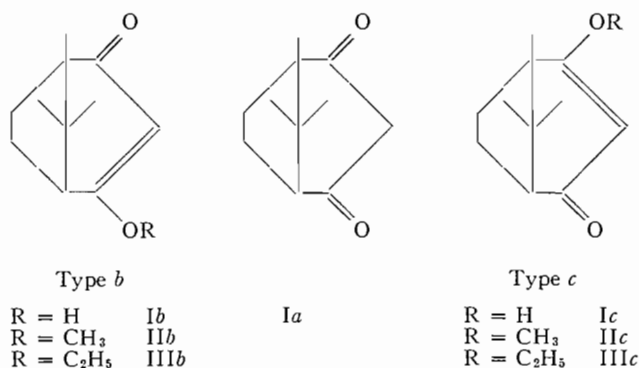
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DÉRIVÉS DU TRIMÉTHYL-1,8,8 BICYCLO[3,2,1]OCTANE

II. SUR LES ÉTHERS CÉTOÉNOLIQUES MÉTHYLIQUES ET ÉTHYLIQUES DE LA TRIMÉTHYL-1,8,8 BICYCLO[3,2,1]OCTANEDIONE-2,4¹

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Nous nous sommes attachés à l'étude des éthers méthyliques et éthyliques de la dicétone I ($I = Ia \rightleftharpoons Ib \rightleftharpoons Ic$) dans le double but d'obtenir des précisions sur l'équilibre dicétonique \rightleftharpoons cétoénolique de I et d'améliorer la synthèse de l'homoépicaïnphre que nous avons décrite avec Richer (1).



Les pourcentages respectifs des éthers du type *b* et du type *c* dans les divers mélanges obtenus ont été déterminés par l'analyse du pouvoir rotatoire de ces mélanges (1) (voir Tableau I). Nous avons résolu à ces fins le mélange obtenu par le mode opératoire 2 et caractérisé les éthers *IIIb* et *IIIc* dont l'un seulement, *IIIb*, était connu (4). L'éther *IIIb*, p.f. 72.5°, a été transformé en homoépicaïnphre, à la manière décrite (1), ce qui établit sans ambiguïté sa structure. Quant à l'éther isomère, p.f. 52°, son pouvoir rotatoire

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