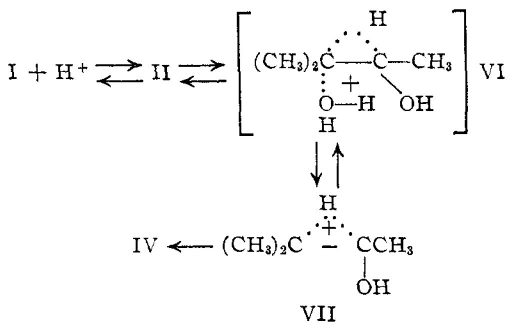

diate VII reacts preferentially with water rather than through rearrangement. Thus, the isotope effect can be rationalized as being larger than that found for hyperconjugation but somewhat smaller than that for a hydride shift.

Bunton and co-workers[27] have calculated from their data that in 1:1 sulfuric acid the partitioning of the ion derived from pinacol strongly favors rearrangement rather than the reversible addition of water. A value of k_{-2}/k_3 *ca.* 1/9 was estimated. In order to test the hypothesis that the isotope effect was characteristic only of the rate-determining ionization step, several runs were made in 1:1 sulfuric acid. The rate constants are recorded in Table II. Experimental difficulties with the kinetic determinations under these conditions were encountered. However, the data do show a marked decrease in the isotope effect to around 1.2. This decrease may be understood also on the basis of the above mechanistic scheme. As the solvating power of the medium increases, the need for stabilization of the ionic intermediate through hydrogen participation decreases. It is to be expected that 1:1 sulfuric acid is a considerably better solvating medium than dilute solutions of aqueous perchloric acid. The decreased need for hydrogen participation in 1:1 sulfuric acid reflects itself in a lowering of the value of the isotope effect.

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ATHENS, OHIO

[CONTRIBUTION FROM THE INSTITUTE FOR CHEMICAL RESEARCH, KYOTO UNIVERSITY]

Isotopic Tracer Studies of the Ketonic Pyrolysis of Sodium Carboxylates

BY RISABURO NAKAI, MICHIYASU SUGII AND HIDEO NAKAO[1]

RECEIVED JULY 28, 1958

The isotopic tracer technique has been applied to a study of the formation of ketones by the pyrolysis of a mixture of sodium acetate and sodium phenylacetate or sodium propionate. The specific radioactivity of the symmetrical ketones produced and that of the recovered carboxylic acids shows an exchange reaction between labeled and non-labeled carboxyl groups.

Bell and Reed[2] have pyrolyzed a mixture of barium acetate-carboxyl-C^{13} and barium formate and suggest a free radical mechanism to account for the exclusive cleavage of the carbon–carbon bond in acetate. By using C^{14} tracer techniques, Lee and Spinks[3] have examined the unsymmetrical ketones produced by the dry distillation of several mixtures of calcium carboxylate and explained the observed facts by an ionic mechanism. They, however, have proposed a concerted process for the decarboxylation, in which the reaction may involve either heterolytic or hemolytic cleavage of the bond concerned.

We have carried out similar studies using a mixture of sodium phenylacetate-1-C^{14} and sodium acetate and a mixture of sodium acetate-1-C^{14} and sodium propionate, respectively. Since an appreciable difference between the fusion temperature and the decomposition temperature was desired, the sodium carboxylates which possess a distinct fusing point were used. The calcium or barium salts decompose without fusing. Pyrolyses were carried out at reduced pressure to avoid decomposition of the ketones. The ketones produced were converted to the corresponding 2,4-dinitrophenylhydrazones. The crude mixture of hydrazones was separated into its components by means of column chromatography and the radioactivity of each was determined. The specific radioactivity of the unsymmetrical ketone, the main product, would indicate the ratio of ease with which the carboxyl group is lost in forming ketone, if the specific activity of the symmetrical ketones is equal to that of the corresponding original acids. Contrary to expectation, the results in experiment A, Table I, indicate that the specific ac-

TABLE I

RADIOACTIVITY OF 2,4-DINITROPHENYLHYDRAZONES

	Reactants	2,4-Dinitrophenylhydrazone, ketone	Specific activity, μc./mmole	% of original activity
(A)	$C_6H_5CH_2C^{14}OONa$		12.60 ± 0.21	100
	CH_3COONa		....	0
		Methyl benzyl	7.04 ± .15	55.8
		Dibenzyl	7.95 ± .17	63.1
		Acetone	4.67 ± .14	37.1
		Na_2CO_3	6.74 ± .15	53.5
(B)	$CH_3C^{14}OONa$		7.68 ± .18	100
	C_2H_5COONa			0
		Methyl ethyl	3.56 ± .12	46.4
		Acetone	4.83 ± .15	62.9
		Diethyl	3.42 ± .10	44.5
		Na_2CO_3	4.15 ± .12	54.0

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[1] Takamine Research Laboratory, Sankyo Co., Ltd., Shinagawa-ku, Tokyo, Japan.

[2] J. Bell and R. I. Reed, *J. Chem. Soc.*, 1383 (1952); 4423 (1955).

[3] C. C. Lee and J. W. T. Spinks, *J. Org. Chem.*, **18**, 1079 (1953).

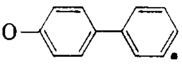
TABLE II

RADIOACTIVITY OF *p*-PHENYL PHENACYL CARBOXYLATE

Expt.	Reactants	Specific activity, μc./mmole	Reac. temp. of mixt., °C.	Reac. time, min.	*p*-Phenyl phenacyl carboxylate[b]	Specific activity, μc./mmole	% of original activity
1	$C_6H_5CH_2C^{14}OONa$	12.6 ± 0.21	310–320	10	$C_6H_5CH_2COOR$	10.80 ± 0.25	85.7
	CH_3COONa	....			CH_3COOR	1.81 ± .08	14.4
					$C_6H_5CH_2COOH$	10.70 ± .22	84.9
2	$C_6H_5CH_2COONa$	....	310–320	15	$C_6H_5CH_2COOR$	2.73 ± .09	35.6
	$CH_3C^{14}OONa$	7.68 ± .18			CH_3COOR	5.05 ± .11	65.8
					$C_6H_5CH_2COOH$	2.72 ± .07	35.6
3	$CH_3C^{14}OONa$	7.68 ± .18	350–360	2	CH_3COOR	7.39 ± .17	96.2
	C_2H_5COONa	....			C_2H_5COOR	0.09 ± .01	1.2
4	$CH_3C^{14}OONa$	7.68 ± .18	350–360	10	CH_3COOR	5.95 ± .19	77.5
	C_2H_5COONa	....			C_2H_5COOR	1.56 ± .09	20.3
5[a]	$CH_3C^{14}OONa$	7.68 ± .18	240–260	10	CH_3COOR	7.69 ± .16	100.0
	C_2H_5COONa	....			C_2H_5COOR	0	0

[a] Experiment at fusing temperature.

[b] $R = CH_2CO$—



tivity of dibenzyl ketone was smaller than that of the sodium phenylacetate and the acetone showed a distinct activity, in spite of careful separation and repeated purifications. Similar results were obtained in experiment B. These facts show that the carboxyl group is interchangeable between the two carboxylates.

The exchange reaction of the carboxyl groups was explored experimentally. Equimolar quantities of two carboxylic acid salts were treated as in the preceding case. However, with a view to avoiding complete decomposition, the mixture of salts was maintained at the decomposition temperature for a time insufficient for complete reaction. The residual mixture of undecomposed acid salts was converted to the corresponding *p*-phenylphenacyl ester and separated into its components by the method of Kirchner, *et al.*[4] The specific radioactivity of the separated esters was determined. The results, shown in Table II, indicate that after the treatment, the specific activity of the labeled carboxylic acid decreased and the originally non-labeled acid showed a distinct radioactivity. The extent of carboxyl exchange increased rapidly with the pyrolytic time. These carboxyl exchange reactions have not been reported previously. In another experiment (5 in Table II), a mixture of the sodium salts of acetic acid-1-C^{14} and non-labeled propionic acid was heated to the fusing temperature and kept at the fused state for 10 minutes. No sodium carbonate or ketone was detected. The residual mixture of undecomposed acid salts was separated as in the preceding case. The *p*-phenylphenacyl acetate possessed the original specific activity and the *p*-phenylphenacyl propionate showed no observable radioactivity. Therefore the carboxyl interchange does not take place in the fused state of the carboxylate.

If the carboxyl exchange reactions relate to the pyrolysis, the sodium carbonate produced might take part in the carbon exchange. Grant and Turner[5] have reported sodium formate–sodium carbonate exchange at 250° and a significant finding that there is no carbon exchange between the sodium acetate-1-C^{14} and sodium carbonate at 250°. Bigeleisen, *et al.*,[6] have pyrolyzed barium adipate admixed with barium carbonate-C^{14} and no activity was detected in the ketone formed. Similar pyrolysis of sodium phenyl acetate in the presence of sodium carbonate-C^{14} was carried out at 250° for 5 minutes. No activity could be detected in the recovered phenyl acetate and in the dibenzyl ketone formed.

Therefore under pyrolytic conditions there is no carbon exchange between carbonate and carboxylate which has at least an α-carbon.

The fact that carbonate does not participate in the carbon exchange supports the view that the carbon–carboxyl cleavage of the carboxylic acid salt is a first step in its pyrolysis. It might be interpreted as a homolytic mechanism rather than an ionic one.

For examination of the gaseous products, a mixture of non-labeled sodium acetate and sodium propionate was pyrolyzed in a similar manner and the liberated gas was analyzed by gas chromatography. Carbon dioxide, carbon monoxide, methane, ethane, propane and butane were detected. The formation of propane and butane may be expected in a free radical process.

Experimental

Pyrolyses.—Equimolar quantities of the two well-dried sodium salts were mixed and ground in a mortar. The mixture was placed in a small distillation flask connected to three wash bottles containing a saturated solution of 2,4-dinitrophenylhydrazine in 2 *N* hydrochloric acid. The flask and a thermocouple were heated in an air-bath. The apparatus was connected to a vacuum pump through the wash bottles and the pyrolyses were carried out at about 20 mm. pressure. The volatile ketones were bubbled through the 2,4-dinitrophenylhydrazine solution and heating was continued until no more precipitation of hydrazones was obtainable. In experiment A, a small amount of oily distillate was obtained which was dissolved in ethanol and converted to the hydrazone. About 30–40 minutes was required to complete the reaction. The residual sodium carbonate was dissolved in water and treated with decolorizing charcoal to remove tarry impurities and converted to barium carbonate by the usual method. The data are summarized in Table III.

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(4) J. G. Kirchner, A. N. Prater and A. J. Haagen-Smit, *Ind. Eng. Chem., Anal. Ed.*, **18**, 31 (1946).

(5) D. G. Grant and H. S. Turner, *Nature*, **165**, 153 (1950).

(6) J. Bigeleisen, A. A. Bothner-By and L. Friedman, THIS JOURNAL, **75**, 2908 (1953).

TABLE III

PYROLYSES OF SODIUM SALTS MIXTURE

Reaction time 30–40 min.

	Reactants	Wt., g.	Fusing temp. of mixt., °C.	Decomp. temp. of mixt., °C.	Distillate	Yield, g., of hydrazones	$BaCO_3$
(A)	$C_6H_5CH_2C^{14}OONa$	1.80	200–250	310–320	0.47	1.29	1.36
	CH_3COONa	0.93					
(B)	$CH_3C^{14}OONa$	1.60	240–260	350–360	..	1.56	2.46
	C_2H_5COONa	1.90					

TABLE IV

CHROMATOGRAPHIC SEPARATION OF 2,4-DINITROPHENYLHYDRAZONES

Mixture, g.	2,4-Dinitrophenylhydrazone	Position of band	Color of band	Yield of pure compound, g.	M.p., °C.
(A) 1.29	Acetone	Upper	Orange	0.06	124
	Methyl benzyl ketone	Middle	Orange	.51	153
	Dibenzyl ketone	Lower	Yellow	.10	108
(B) 1.56	Acetone	Upper	Orange	.13	124
	Methyl ethyl ketone	Middle	Orange	.57	115
	Diethyl ketone	Lower	Red	.11	155

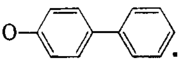
TABLE V

YIELD OF *p*-PHENYL PHENACYL CARBOXYLATE

Expt.	Reactants	Wt., g.	Reaction temp. of mixt., °C.	Reacn. time, min.	*p*-Phenyl phenacyl carboxylate[b]	Yield, g.	M.p., °C.
1	$C_6H_5CH_2C^{14}OONa$	0.87	310–320	10	$C_6H_5CH_2COOR$	0.26	89
	CH_3COONa	.45			CH_3COOR	.31	111
					$C_6H_5CH_2COOH$	.19	76
2	$C_6H_5CH_2COONa$	.87	310–320	15	$C_6H_5CH_2COOR$	.30	89
	$CH_3C^{14}OONa$	.45			CH_3COOR	.29	111
					$C_6H_5CH_2COOH$	.12	76
3	$CH_3C^{14}OONa$	.45	350–360	2	CH_3COOR	.42	111
	C_2H_5COONa	.53			C_2H_6COOR	.49	102
4	$CH_3C^{14}OONa$	.60	350–360	10	CH_3COOR	.43	111
	C_2H_5COONa	.70			C_2H_6COOR	.47	102
5[a]	$CH_3C^{14}OONa$	.45	240–260	10	CH_3COOR	.45	111
	C_2H_5COONa	.53			C_2H_5COOR	.41	102

[a] Experiment at fusing temperature.

[b] R = CH_2CO—



A mixture of 5 g. of sodium acetate and 5.9 g. of sodium propionate was treated as in the preceding experiments and the issuing gas was analyzed by elution gas chromatography (carrier, hydrogen). Carbon monoxide, methane, carbon dioxide and ethane were identified in the proportion of 1:2:1:1 (active carbon column) and propane and butane were identified in the proportion of 0.04:0.04 (dibenzyl ether column).

Chromatographic Separation of Ketones.—The procedure of Roberts and Green[7] was modified. Merck silicic acid mixed with Super-cel in a 4 to 1 ratio by weight was used as the adsorbent. In order to remove a small amount of an impurity, 10 g. of alumina was packed at the top of the silicic acid–Super-cel adsorbent. The crude mixture of 2,4-dinitrophenylhydrazones of (A) was dissolved in 10 ml. of dry benzene, adsorbed on a 3 × 70 cm. column, and developed with the same solvent. After the development the column consisted of three bands. The zones were cut into sections, eluted with ethanol, and the solvent was evaporated to dryness. The residues were readsorbed to remove traces of unidentified compounds, and recrystallized from ethanol. Mixed melting points with known compounds were used to identify them. In a similar manner, the crude mixture of hydrazones of (B) was successfully separated into its components. The data are summarized in Table IV.

Exchange Reaction of Carboxyl Group between Two Acids.—Equimolar quantities of two sodium salts were treated precisely as in the preceding experiment. However, to avoid complete decomposition, the mixture was maintained for a definite period of time at the decomposition temperature. The residual undecomposed mixture was dissolved in water, treated with decolorizing charcoal and evaporated to dryness. When the phenylacetate was used, the unchanged mixture was dissolved in water, washed with ether and treated with decolorizing charcoal. The filtrate was acidified with 2 *N* hydrochloric acid and the precipitated phenylacetic acid was recrystallized from boiling water. The mother liquor from the phenylacetic acid was neutralized with *N* sodium hydroxide and evaporated to dryness. The residues were converted to the *p*-phenylphenacyl esters according to Drake, *et al.*[8] A benzene solution of the crude ester mixture was passed through a short alumina column which adsorbed some highly fluorescent impurities that were removed with difficulty by silicic acid. The eluted mixture was separated into its components by silicic acid chromatography applying the technique of Kirchner, *et al.*[4] In the case of acetate and phenylacetate, the latter appeared at the lower band of the column. To purify further, the separated esters were readsorbed and recrystallized from ethanol. The data are summarized in Table V. In experiment 5, the reaction was maintained at the fusion temperature and neither the fused mass nor the 2,4-dinitrophenylhydrazine solution through which the reaction gas was passed showed turbidity.

Pyrolysis of Acid Salt Admixed with Carbonate.—A mixture of 1.0 g. of sodium carbonate-C^{14} (1.29 ± 0.05 μc./mmole) and 1.6 g. of sodium phenylacetate was maintained at the decomposition temperature (240–250°)[9] for 5 minutes under a pressure of 20 mm. The residual unchanged acid and the distilled ketone were separated in the preceding manner. There were obtained 0.1 g. of phenylacetic acid

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[7] J. Roberts and C. Green, *Ind. Eng. Chem., Anal. Ed.*, **18**, 335 (1946).

[8] N. L. Drake and J. Bronitsky, THIS JOURNAL, **52**, 3715 (1930).

[9] In the presence of sodium carbonate the decomposition temperature of sodium phenylacetate was lowered from 310° (the latter alone) to 240–250°.

and 0.62 g. of dibenzyl ketone 2,4-dinitrophenylhydrazone. Both compounds possessed no observable radioactivity.

Isotopic Assay.—For the determination of radioactivity, the sodium acetate was converted into *p*-nitrobenzyl acetate according to the direction of Bell and Reed.[2] The sodium phenylacetate was also converted into the free acid for combustion. All samples assayed were burned by a dry combustion method and converted to barium carbonate. The activity was counted at infinite thickness with a G-M. counter tube and compared with the count of a standard barium carbonate.

Acknowledgments.—The authors wish to thank Mr. Yasuzi Maeno for his assistance and Professor Y. Takezaki for the gas chromatographic analyses.

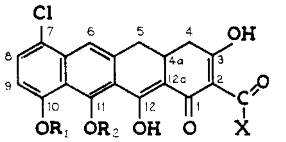
TAKATSUKI, OSAKA-FU, JAPAN

COMMUNICATIONS TO THE EDITOR

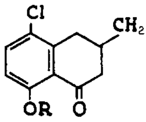
TOTAL SYNTHESIS OF TETRACYCLINES. I. (±)-DEDIMETHYLAMINO-12a-DEOXY-6-DEMETHYLANHYDROCHLOROTETRACYCLINE

Sir:

Since the structure elucidation in 1952 of oxytetracycline[1] and of chlorotetracycline,[2] synthetic efforts have led to certain dicarbocyclic degradation products[3] and to model substances having structural similarities to portions of the tetracycline molecule. More recently Shemyakin[4] and Muxfeldt[5] have described the preparation of tricyclic intermediates suitable for further synthetic elaboration. We now report the total synthesis of biologically active (±)-dedimethylamino-12a-deoxy-6-demethylanhydrochlorotetracycline (I) and its comparison with a sample prepared from the natural antibiotic 6-demethylchlorotetracycline[6]



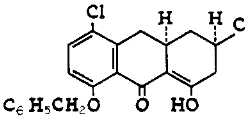
I $R_1 = R_2 = H$, $X = NH_2$
XII $R_1 = CH_2C_6H_5$, $R_2 = CH_3$, $X = OC_2H_5$



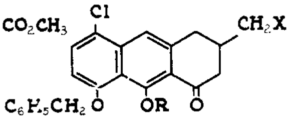
II $R = CH_3$, $X = CO_2H$
III $R = CH_3$, $X = COCl$
IV $R = CH_3$, $X = CHO$
V $R = H$ $X = CH(CH_2CO_2H)_2$
VI $R = CH_2C_6H_5$, $X = CH(CH_2CO_2CH_3)_2$

Alkylation of diethyl sodiomalonate with 2-chloro-5-methoxybenzyl bromide, prepared by peroxide-catalyzed bromination of 4-chloro-3-methylanisole with N-bromosuccinimide, gave the benzylmalonic ester (b.p. 147–155° (0.3 mm.); found: C, 57.38; H, 6.32). Reduction of the latter with lithium aluminum hydride produced the corresponding 1,3-diol, which was converted by standard methods to the bis-methanesulfonate (m.p. 75–77°; found: C, 40.59; H, 5.09) and thence to the dinitrile. Alkaline hydrolysis to the substituted benzylglutaric acid and subsequent ring closure with polyphosphoric acid produced the tetraloneacetic acid II (m.p. 193–196°; found: C, 57.69; H, 4.98).

Modified Rosenmund reduction of the acid chloride III gave 82% of the aldehyde IV (m.p. 89–91°; found: C, 61.63; H, 5.40). Piperidine-catalyzed condensation of IV with excess cyanoacetamide yielded a crystalline dicyanodiamide, which upon acid hydrolysis underwent demethylation to the phenolic diacid V (m.p. 181–182°; found: C, 56.45; H, 5.30). Reaction of V with benzyl chloride and subsequent esterification produced the diester VI (m.p. 62–63°; found: C, 65.10; H, 6.04). The latter was cyclized by sodium hydride in toluene to a crystalline tricyclic ester (m.p. 118–121°; found: C, 67.47; H, 5.58; Cl, 8.85; $\lambda_{\max}^{\mathrm{CH_3OH}}$ 343, 262, (225) mμ, log ε 4.19, 3.77, (4.31); $\lambda_{\max}^{0.1\,N\,\mathrm{NaOH}}$ 359, (260), 219 mμ, log ε 4.15, (3.92), 4.36) tentatively assigned relative stereochemistry VII on conformational grounds.



VII



VIII $R = H$, $X = CO_2CH_3$
IX $R = CH_3$, $X = CO_2CH_3$
X $R = CH_3$, $X = CO_2H$
XI $R = CH_3$, $X = COCH(CO_2C_2H_5)_2$

Angular bromination followed by dehydrobromination in collidine converted VII to the highly fluorescent phenol VIII, which was further transformed by the action of dimethyl sulfate and potassium carbonate into the methyl ether IX and thence to the tricyclic acid X (m.p. 176–177°; found: C, 67.72; H, 5.06; OCH_3, 7.27; $\lambda_{\max}^{\mathrm{MeOH}}$ 377, 322, 309, 260 mμ, log ε 3.74, 3.53, 3.60, 4.55). Entry to the tetracyclic series was effected by converting acid X to the acylmalonate[7] XI, which was cyclized by sodium hydride in toluene to the ester XII[8] (m.p. 169–171°; found: C, 66.85; H, 5.08; OCH_3, 11.11; $\lambda_{\max}^{\mathrm{MeOH(H^+)}}$ 390, 322, 266, 227, log ε 4.38, 4.02, 4.38, 4.49).

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(1) F. A. Hochstein, C. R. Stephens, L. H. Conover, P. P. Regna, R. Pasternack, P. N. Gordon, F. J. Pilgrim, K. J. Brunings and R. B. Woodward, THIS JOURNAL, **75**, 5455 (1953).

(2) (a) C. R. Stephens, L. H. Conover, R. Pasternack, F. A. Hochstein, W. T. Moreland, P. P. Regna, F. J. Pilgrim, K. J. Brunings and R. B. Woodward, *ibid.*, **74**, 4976 (1952); **76**, 3568 (1954); (b) C. W. Waller, B. L. Hutchings, R. W. Broschard, A. A. Goldman, C. F. Wolf and J. H. Williams, *ibid.*, **74**, 4981 (1952).

(3) (a) L. Conover, *ibid.*, **75**, 4017 (1953); (b) R. B. Woodward and E. F. Ullman, unpublished observations; E. F. Ullman, Ph.D. thesis, Harvard University, 1956; (c) Z. Horii, Y. Tamura and K. Tanaka, *Pharm. Bull.* (Tokyo), **5**, 284–285 (1957).

(4) M. M. Shemyakin, M. N. Kolosov, M. G. Karapetyan and E. S. Chaman, *Proc. Acad. Sci. U.S.S.R., Sect. Chem.*, **112**, 669 (1957).

(5) H. Muxfeldt, *Abhandlungen der Braunschweigischen Wissenschaftlichen Gesellschaft.*, **10**, 1 (1958).

(6) J. R. McCormick, N. O. Sjolander, U. Hirsch, E. R Jensen, A. P. Doerschuk, THIS JOURNAL, **79**, 4561 (1957).

(7) D. S. Tarbell and J. R. Price, *J. Org. Chem.*, **21**, 144 (1956); **22**, 245 (1957).

(8) Zinc dust distillation of the ester gave naphthacene.