Scientific Type) at 10 cm. distance isomerized only 2% of neo-α-carotene U in thirty minutes; some all-*trans* form, neo **X**, and neo **Y** appeared in the Tswett column. Solutions of the neo-α-carotenes V, W, and B were insolated for forty-five minutes. The colorimetric ratios are summarized in Table VII.

TABLE VII

RELATIVE COLORIMETRIC VALUES OF SOME MEMBERS OF THE α- AND β-CAROTENE SETS FORMED BY FORTY-FIVE MINUTES INSOLATION IN PETROLEUM ETHER SOLUTION

Starting material	Relative colorimetric values (% of the recovered pigment) neo U	neo V	neo W	neo X	neo Y	all-*trans*	neo A	neo B	neo C...
				α-Carotene					
Neo U	64.5	1.5	3.5	2	3	24	—	1.5	—
Neo V	33	43	4	2	—	16	—	2	—
Neo W	7.5	5	32.5	1	—	41	4	7.5	1.5
All-*trans*	1.5	—	2	—	—	93.5	—	2.5	0.5
Neo B	1.5	—	34	—	—	56.5	—	8	—
				β-Carotene					
Neo U	36.5	—				55		6	2.5
All-*trans*	1	—				98		1	—
Neo B	27	2.5				60		5	5.5

(h) **Sequence of Zones Obtained by Iodine Isomerization of a Mixture of α- and β-Carotene.**—Since the two all-*trans* carotenes yield isomers with both increased and decreased adsorption affinities, a great number of zones overlap in a chromatogram. After catalysis the pigment mixture was developed on calcium hydroxide with petroleum ether containing 2% acetone. The chromatogram did not contain colorless sections; nevertheless, sections of different colors enabled the experimenter to cut out suitable zones. The addition of iodine to the solution of each pigment in the spectroscopic cell established the set to which the isomer belonged. This procedure was the basis for the chromatographic investigation of suitable binary mixtures. Such pairs were submitted to a prolonged development with petroleum ether. The sequence established in the order of decreasing adsorption affinity follows: neo-β-carotene U, neo-β-carotene V, neo-α-carotene U, all-*trans*-β-carotene, neo-α-carotene V, neo-β-carotene B, neo-β-carotene E, neo-α-carotene W, neo-β-carotene F, all-*trans*-α-carotene, neo-α-carotene B, and neo-α-carotenes C, D, etc.

Summary

Some data are given concerning *cis–trans* isomerization in the stereoisomeric α-carotene set as compared with the β-carotene, lutein, and lycopene sets. Ten *cis–trans* isomeric α-carotenes were observed which adsorb partly above, partly below the all-*trans* pigment in the Tswett column. Photo-isomerization experiments are described. The contribution of some stereoisomers to the *cis*-peak of the iodine equilibrium mixture was determined. Some spectral data served as a basis for a discussion of configurations.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF OCCIDENTAL COLLEGE]

The Use of Potassium *t*-Amyloxide for the Alkylation of Acetoacetic Ester and its Alkyl Substitution Products

BY W. B. RENFROW, JR.

Alkylation of acetoacetic ester with sodium ethoxide in ethanol and an alkyl bromide gives yields of 70–80% with *n*-alkyl bromides,[1] but secondary alkyl bromides and bromides with a branch in the chain at the β-position (*i. e.*, isobutyl) generally give less than a 30% yield[2] of mono-substituted acetoacetic ester. Moreover, the further alkylation in the usual way of a mono-α-substituted acetoacetic ester with an *n*-alkyl bromide generally gives less than a 40% yield of disubstituted acetoacetic ester.[3]

Theoretical considerations indicated that the yields in the less favorable cases could be improved by the use of an alkoxide of greater proton-affinity than sodium ethoxide. Potassium *t*-amyloxide is a conveniently available base which is stronger than sodium ethoxide,[4] and was selected for investigation.

Table I gives the results obtained. The course of the reaction was followed by titration of aliquots with acid, and the approximate times were determined at the temperature of the refluxing solutions for one-half of the base to react.

Comparison of the data in Table I with similar data using sodium ethoxide[1,5,6] shows that potassium *t*-amyloxide in *t*-amyl alcohol and sodium ethoxide in ethanol are of about equal effectiveness for the alkylation of ethyl acetoacetate with primary, straight-chain bromides. However, potassium *t*-amyloxide gives considerably better yields of ethyl α-isopropylacetoacetate, ethyl α-isobutylacetoacetate, ethyl α,α-diethylacetoacetate and ethyl α,α-dibutylacetoacetate than can be obtained by use of sodium ethoxide in ethanol.[2,7,8]

(1) For the usual method of alkylation, see: Gilman, Blatt, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, New York, N. Y., 1941, p. 248.

(2) In the present investigation ethyl isopropylacetoacetate and ethyl isobutylacetoacetate were obtained in 20–25% yields by the method described in (1).

(3) Hess and Bappert, *Ann.*, **441**, 151 (1925), obtained a 38% yield of α,α-di-*n*-butylacetoacetic ester under certain conditions. Under other conditions the product was almost exclusively ethyl di-*n*-butylacetate. Compare also Billon, *Ann. chim.*, **7**, 355 (1927).

(4) McEwen, THIS JOURNAL, **58**, 1124 (1936), found the following relative values for *pKa*: methanol, 16; ethanol, 18; *t*-amyl alcohol, 19.

(5) Michael, *J. prakt. Chem.*, **72**, 553 (1905).

(6) Locquin, *Bull. soc. chim.*, **31**, 758 (1904).

(7) Conrad and Limpach, *Ann.*, **192**, 153 (1878).

TABLE I

RESULTS OF ALKYLATIONS USING KO—C(CH$_3$)$_2$—C$_2$H$_5$ IN HO—C(CH$_3$)$_2$—C$_2$H$_5$

CH$_3$—C(=O)—C(R)(H)—C(=O)—OEt (R =)	R'Br (R' =)	Reaction half-time (minutes)	Yield of CH$_3$C(=O)—C(R)(R')—C(=O)—OEt (per cent)	Boiling range °C.	Mm.	Ref.
H	Ethyl	10	80	96–98	26	5
H	*n*-Butyl	15	73	110–114	14–15	1
H	Isoamyl	20	72	120–123	15–16	6
H	Isobutyl	100	61	99–103	13–14	9
H	Isopropyl	200	50	200–203	748	10
Ethyl	Ethyl	10	75	96–99	13–14	7
n-Butyl	*n*-Butyl	15	70	143–147	18–19	3

The superiority[8] of potassium *t*-amyloxide over sodium ethoxide in ethanol is considered to be due mainly to two factors: (1) the stronger base causes less shift of the following equilibrium to the right (reverse Claisen condensation[11])

$$CH_3COCRR'CO_2C_2H_5 + HOR'' \underset{}{\overset{KOR''}{\rightleftharpoons}} CH_3CO_2R'' + HCRR'CO_2C_2H_5$$

and (2), the stronger base makes available a higher concentration of the desired metallic enolates of acetoacetic esters by shifting the following equilibrium further to the right.

$$CH_3COCHR'CO_2C_2H_5 + KOR'' \rightleftharpoons (CH_3COR'CO_2C_2H_5)K + HOR''$$

A slow rate of alkylation (as with isopropyl and isobutyl bromides) permits greater reversal of the Claisen condensation by necessitating a prolonged refluxing of acetoacetic esters with alcohol and alkoxide. The α,α-disubstituted acetoacetic esters are especially susceptible to cleavage by sodium ethoxide in ethanol and this side reaction is very troublesome when the usual alkylation procedure is followed.[3] Since it has been shown that a strong base favors the Claisen condensation[11b] (and hence should oppose reversal of the reaction), the higher yields obtained by use of the stronger base are probably mainly due to this factor.

The second factor is probably not significant in the alkylation of ethyl acetoacetate, since this compound is a sufficiently strong acid[12] to be converted almost completely into its enolate by means of sodium ethoxide. This factor may be of some importance, however, in the alkylation of more weakly acidic monosubstituted acetoacetic esters.

Experimental

The technical grade of *t*-amyl alcohol was refluxed for five hours with 2% of its weight of sodium, allowed to stand overnight, decanted through a plug of glass wool and distilled rapidly until the boiling point reached about 106°. The distillate was refluxed for four hours with 1% its weight of sodium and distilled. The fraction boiling at 100–100.8° (747 mm.) was collected as pure *t*-amyl alcohol. This amounted to about 73% of the starting material, and had d^{20}_4 0.809.

Ethyl acetoacetate was purified by fractionation through a 20-cm. column packed with glass helices. The fraction boiling at 83–85° (24 mm.) was used.

The alkyl bromides were thoroughly extracted with concentrated sulfuric acid, washed with bicarbonate solution, dried (calcium chloride) and fractionated.

Experiments were made using from 0.1 to 1.0 gram-atom of potassium. The most convenient amount was about 0.3 gram-atom, and the general procedure was as follows: Potassium (11.7 g., 0.3 gram-atom) was dissolved with stirring at reflux temperature in *t*-amyl alcohol (170 ml.). When larger amounts of potassium were added all at once, external cooling of the flask was usually necessary to prevent too violent refluxing. The solution was cooled (inert atmosphere) to room temperature, ethyl acetoacetate (42.9 g., 0.33 mole) was added and the solution stirred for about two minutes. The alkyl bromide (0.33 mole) was then added and the solution was refluxed and stirred until 90–100% of the base had reacted (usually about three hours).

The reaction mixture was diluted with water (about 100 ml.) and acidified with acetic acid (litmus). The organic layer was separated and distilled at atmospheric pressure until the boiling point reached 110°. The cooled residue was filtered and the filtrate was fractionated through a column packed with glass helices, and 10 to 20 cm. in length, depending upon the boiling point of the product. The columns were equipped with heaters to prevent excessive flooding. Ethyl ethylacetoacetate was further purified before fractionation by extracting it with aqueous sodium bisulfite (20%) to remove excess ethyl acetoacetate.

The procedure was the same for the alkylation of α-substituted acetoacetic esters, except that equivalent amounts of potassium and ester were used. A 10% excess of alkyl bromide was used in all cases.

The rate at which the alkali disappeared was determined as follows: After addition of the alkyl halide, 1.0-ml. aliquots were removed from time to time and added to ethanol (15 ml.) containing "Nitrazine"[13] indicator solution (2

(8) Other improved methods of alkylation that have been suggested involve the use of non-hydroxylic solvents: Wallingford, THIS JOURNAL, **64**, 580 (1942); Elderfield, *J. Org. Chem.*, **4**, 370 (1939); **6**, 57 (1941).

(9) Tafel and Jurgens, *Ber.*, **42**, 2555 (1909).

(10) Hauser and Breslow, THIS JOURNAL, **62**, 2611 (1940).

(11) (a) Concerning the reversibility of the Claisen condensation, see: Beckmann and Adkins, THIS JOURNAL, **56**, 1119 (1934). (b) For a discussion of the role of the base in the Claisen condensation, see: Hauser and Renfrow, THIS JOURNAL, **59**, 1823 (1937); **60**, 463 (1938).

(12) Goldschmidt and Oslan, *Ber.*, **33**, 1146 (1900), report the ionization constant of ethyl acetoacetate to be 2.0×10^{-11}.

(13) A solution of sodium dinitrophenylazo-naphthol disulfonate sold under the trademark of "Nitrazine" by E. R. Squibb and Sons, New York, N. Y.

TABLE II

RESULTS OF KETONIC HYDROLYSES

Ketone	Boiling range °C.	Mm.	Yield, %	Melting point semicarbazone, °C.	Ref.
$CH_3(CH_2)_2COCH_3$	99–102	747	70	110	15
$CH_3(CH_2)_4COCH_3$	148–151	747	75	126–127	15
$(CH_3)_2CHCH_2COCH_3$	114–120	746	36	132–135	15
$(CH_3)_2CH(CH_2)_2COCH_3$	141–142	746	60	142–143	16
$(CH_3)_2CH(CH_2)_3COCH_3$	162–164	746	77	153–154	17
$(CH_3CH_2)_2CHCOCH_3$	135–139	746	45	98–99	18
$(CH_3CH_2CH_2CH_2)_2CHCOCH_3$	104–107	22	64	109[a]	3

[a] Apparently a new compound. Analyzed by method of Veibel, *Bull. soc. chim.*, **41**, 1410 (1917). Calculated for $C_{12}H_{25}ON_3$: $^1/_3$N, 6.16. Found: $^1/_3$N, 6.11.

drops). The solution was titrated with 0.100 *N* hydrochloric acid until the blue color changed to yellow. Since aliquots taken toward the end of the reaction required small volumes of titrating solution, water was added so that approximately equal volumes of ethanol and water were present at the end-points of all titrations.

The structure of alkylation products was confirmed by ketonic hydrolysis. The mono-substituted acetoacetic esters were hydrolyzed with aqueous sodium hydroxide (5%). The esters were first stirred with the alkali (1.5 moles to 1 of ester) for four hours at room temperature, after which the mixture was refluxed for about six hours. The ketones were removed from the cooled solution by ether extraction, the extracts were dried, the solvent was removed and the residue was fractionally distilled. The α,α-disubstituted acetoacetic esters were very resistant to hydrolysis. The following procedure, of many that were tried,[14] gave the best results: a solution of ethyl α,α-dibutylacetoacetate (26 g., 0.107 mole) in methanol (100 ml.) and water (20 ml.) containing potassium hydroxide (8 g., 0.14 mole) was refluxed for four hours. Additional potassium hydroxide (8 g.) and water (10 ml.) were added and the refluxing was continued for eight hours longer. The mixture was distilled from a water-bath, and when 105 ml. of distillate had been removed the residue was transferred to a separatory funnel. Water (25 ml.) was added and the mixture was thoroughly shaken; three layers separated. The lower layer was potassium carbonate solution; the middle layer yielded α-butylcaproic acid (3.7 g.) on acidification; and fractionation of the upper layer gave α,α-dibutylacetone (11.6 g.). The results of the ketonic hydrolyses are summarized in Table II.

(14) The method of Connor and Adkins (THIS JOURNAL, **54**, 3420 (1932)) could not be tried because the equipment was not available. α,α-Dibutylacetoacetic ester was recovered unchanged after it was stirred for six hours at 150–170° with 85% phosphoric acid (Dehn and Jackson, THIS JOURNAL, **55**, 4284 (1933)). Attempts to induce an ester interchange by refluxing α,α-dibutylacetoacetic ester with formic or acetic acid and zinc chloride were unsuccessful.

Summary

1. A procedure is described for the alkylation of acetoacetic esters, by action of potassium *t*-amyloxide in *t*-amyl alcohol and alkyl bromides.

2. The method was found to be advantageous for the preparation of certain α,α-disubstituted acetoacetic esters.

(15) Shriner and Fuson, "Identification of Organic Compounds," John Wiley and Sons, New York, N. Y., 1940, p. 221.
(16) Freylon, *Ann. chim.*, (8) **19**, 559 (1910).
(17) Wallach, *Ann.*, **381**, 86 (1911).
(18) Bardan, *Bull. soc. chim.*, **49**, 1875 (1931).

LOS ANGELES, CALIFORNIA
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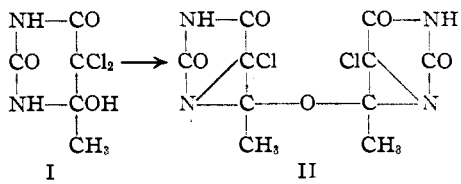
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, YALE UNIVERSITY]

Reactions Characterizing the Oxide of 6-Methyl-6-oxy-5-chloro-1,5-bicyclouracil[1]

BY TREAT B. JOHNSON[2]

The formula adopted to interpret the constitution of the 1,5-bicyclouracil derivative, under discussion in this paper, is expressed graphically in no. II. This cyclo-pyrimidine is produced in excellent yield by digestion of 5,5-dichloro-6-hydroxy-6-methylhydrouracil (I) with concentrated hydrochloric acid.[3]



I II

The specific reactions pertaining to this first representative of a new type of pyrimidine compound, which the author is prepared to discuss at this time, are reported below under the two headings of (a) Reduction and (b) Oxidation Reactions, respectively.

Reduction Reactions

The 1,5-bicyclouracil derivative (II) loses its characteristic bicyclo structure on reduction and reverts to the constitution of a true uracil derivative. Interaction with stannous chloride and hydrochloric acid leads to the quantitative formation of 5-chloro-6-methyluracil, while warming with hydriodic acid and red phosphorus removes

(1) Researches on Pyrimidines. CLXXXI. Experimental work conducted in the Bethwood Research Laboratory, Bethany, Connecticut.

(2) This research was supported in part by a grant from the Research Committee of the Council on Pharmacy and Chemistry, American Medical Association (Grant No. 423).

(3) Johnson, THIS JOURNAL, **65**, 1220 (1943).