gent must have involved in the main the lower level of the reducing equivalents. From the total of these results (see table) a relatively facile reducibility of the halogen of the halohydrin as compared with the reducibility of an ordinary alkyl halide is demonstrated. There may be some variation in the ratio of 1,2-reduction of the carbonyl group and direct or 1,4-reductive elimination of bromine from the bromo ketone or bromohydrin, depending on which hydrogens of the reducing agent are involved, but because of the facility of reduction of the bromohydrin this problem may not be easy to investigate. From these experiments it seems probable at the first reducing level of the reagent, and certain at the lower level, that 1,2-reduction of the carbonyl group is the dominant primary reaction in the three cases studied. Further studies on this problem are in progress.

Experimental

In a typical experiment a solution of 0.02 mole of the α-haloketone in 100 ml. of dry ether was added dropwise slowly to a stirred solution of lithium aluminum hydride in 100 ml. of dry ether. Stirring was continued for a half to one hour after the addition was complete. Water (25 ml.) was added, followed by 3 *N* hydrochloric acid, and the ether layer was separated, washed, dried over sodium sulfate and evaporated. The residue was recrystallized from ligroin.

Summary

Three typical α-haloketones undergo chiefly 1,2-reduction at the carbonyl group as the first step in the reaction with lithium aluminum hydride. Subsequent reduction of the bromine from a typical bromohydrin, proceeds with somewhat greater difficulty, by direct displacement, but occurs more easily than reduction of ordinary alkyl bromide.

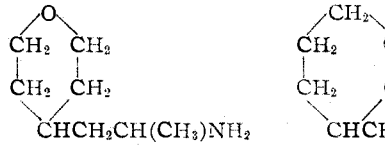
CHARLOTTESVILLE, VA. RECEIVED MAY 15, 1950

[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY, UNIVERSITY OF VIRGINIA]

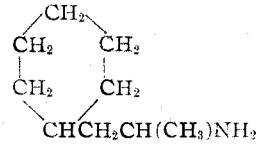
Some Derivatives of Tetrahydropyran as Potential Pharmacodynamic Agents. II[1]

BY ALFRED BURGER, LENNOX B. TURNBULL[2] AND J. GRAY DINWIDDIE, JR.

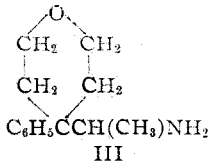
4-(1-Hydroxy-2-piperidinoethyl)-tetrahydropyran exhibits in rats a marked analgetic effect in a large proportion of the animals tested.[1] It appeared of interest to investigate whether a favorable pharmacodynamic behavior would be found in other derivatives of tetrahydropyran which contain suitable functional groups. We have prepared three types of compounds for this purpose. First, 1-(4-tetrahydropyranyl)-2-aminopropane (I) was to be compared with the isosteric local vasoconstrictor agent 1-cyclohexyl-2-aminopropane (II). Second, 1-(4-phenyl-4-



I

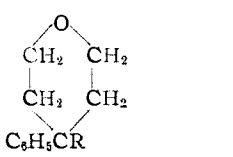


II

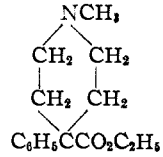


III

tetrahydropyranyl)-ethylamine (III) was to demonstrate the effect of incorporating the tetrahydropyran ring in derivatives of 1-phenyl-2-aminopropane. The third type included a series of 4-dialkylaminoacetyl-4-phenyltetrahydropyran (IV) and 1-(4-phenyltetrahydropyranyl)-2-dialkyl aminoethanol (V) derivatives which could be interpreted as analogs of the drug, Demerol (VI), the basic function having been removed into the side chain.



IV, R = $COCH_2NR_2$
V, R = $CHOHCH_2NR_2$



VI

1-(4-Tetrahydropyranyl)-2-aminopropane (I) was synthesized in seven steps starting from 4-carboxytetrahydropyran (VII). This acid was reduced to 4-tetrahydropyranylmethanol (VIII) with lithium aluminum hydride, the carbinol was converted to 4-tetrahydropyranylmethyl bromide (IX) and the latter was condensed with diethyl sodio methylmalonate. By hydrolyzing and decarboxylating the resulting diethyl methyl-(4-tetrahydropyranylmethyl)-malonate (X), α-methyl-β-(4-tetrahydropyranyl)-propionic acid (XI) was obtained which was degraded to the amine (I) by the Curtius method.

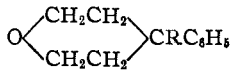
$C_5H_9O{\cdot}CO_2H \longrightarrow C_5H_9O{\cdot}CH_2OH \longrightarrow$
VII VIII
$C_5H_9OCH_2Br \longrightarrow C_5H_9O{\cdot}CH_2C(CH_3)(CO_2C_2H_5)_2 \longrightarrow$
IX X
$C_5H_9O{\cdot}CH_2CH(CH_3)CO_2H \longrightarrow$ I
XI

1-(4-Phenyl-4-tetrahydropyranyl)-ethylamine (III) was obtained conveniently by converting

(1) First article: Harnest and Burger, THIS JOURNAL, **65**, 370 (1943).

(2) du Pont Fellow, 1948-1950.

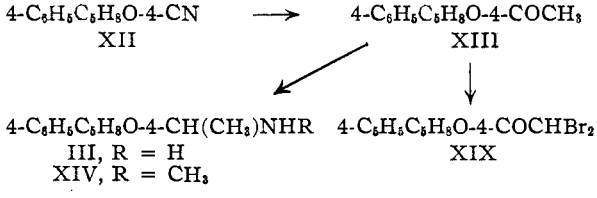
TABLE I

DERIVATIVES OF 4-PHENYLTETRAHYDROPYRAN 

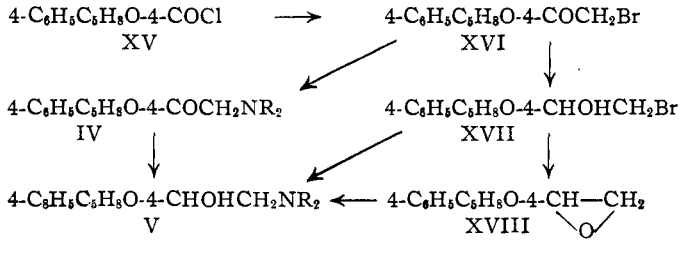
R	Appearance colorless	Solvent of crystn.	M. p., °C. (cor.) or b. p., °C. (mm.)	Yield, %	Molecular compn.	Analyses, % Calcd.	Found
$COCH_3$	Needles	Ligroin	59.5–60.5	64	$C_{13}H_{16}O_2$	C, 76.44	76.39
			133–141 (2)			H, 7.90	7.60
$COCH_2Br$	Crystals	Ligroin	48.5–49.5	87	$C_{13}H_{15}BrO_2$	C, 55.14	55.78
						H, 5.34	5.60
$COCHBr_2$	Crystals	Ligroin	97–98	59	$C_{13}H_{14}Br_2O_2$	C, 43.12	43.30
						H, 3.90	3.93
$CHOHCH_2Br$	Prisms	Ligroin	103.5–104.5	72	$C_{13}H_{17}BrO_2$	Br, 28.02	27.75
$CHCH_2O$	Oil		125–130 (0.8)	62			
$CH(NH_2)CH_3 \cdot HCl$	Prisms	EtOH–Et_2O	241–243	67	$C_{13}H_{19}NO \cdot HCl$	C, 64.58	64.22
						H, 8.34	8.00
						N, 5.79	5.68
$CH(NHCOC_6H_5)CH_3$	Crystals	MeOH	129–130		$C_{20}H_{23}NO_2$	N, 4.53	4.44
$CH(NHCH_3)CH_3 \cdot HCl$	Needles	EtOH–Et_2O	267.5–268.5	14	$C_{14}H_{21}NO \cdot HCl$	N, 5.48	5.47
$COCH_2N(C_2H_5)_2 \cdot$diliturate	Crystals	H_2O	209.5–213.5		$C_{21}H_{26}N_4O_7$	N, 12.49	12.40
$COCH_2NC_5H_{10} \cdot$diliturate	Crystals	H_2O	205–206		$C_{22}H_{28}N_4O_7$	N, 12.17	11.82
$CHOHCH_2NC_5H_{10} \cdot HCl$[a,b]	Prisms	EtOH–Me_2CO	224–227	37	$C_{18}H_{27}O_2N \cdot HCl$	N, 4.30	4.20
$COCH_2NC_4H_8O \cdot$diliturate	Crystals	H_2O	220.3 (dec.)		$C_{21}H_{26}N_4O_8$	N, 12.12	11.93
$CHOHCH_2NC_4H_8O$[b]	Oil		158–160 (0.5)				
$CHOHCH_2NC_4H_8O \cdot HCl$	Crystals	EtOH–EtOAc	210–211.5		$C_{17}H_{25}NO_3 \cdot HCl$	C, 62.28	62.21
						H, 7.99	8.00
$CHOHCH_2N(CH_2CH_2CH_3)_2 \cdot HCl$[a]	Prisms	EtOAc	157–165	20	$C_{19}H_{31}NO_2 \cdot HCl$	C, 67.48	67.23
						H, 9.32	9.07

[a] Prepared by method (a). [b] Prepared by method (b).

4-cyano-4-phenyltetrahydropyran[3] (XII) to 4-acetyl-4-phenyltetrahydropyran (XIII) and subjecting the latter to a Leuckart reaction with ammonium formate. The secondary amine (XIV) resulted in a similar way when methylammonium formate was used.



For the preparation of compounds of type (IV) and V, 4-phenyl-4-tetrahydropyranoyl chloride (XV)[3] was treated with diazomethane and the resulting diazo ketone was converted to the bromo ketone (XVI). The route to the amino alcohols (V) from this point followed three courses. Secondary amines were condensed with the bromo ketone to yield the amino ketones (IV), which were reduced with aluminum isopropoxide. The bromo ketone (XV) was also reduced to the bromohydrin (XVII) followed by condensation with appropriate secondary amines, or elimination of hydrogen bromide from XVII by alkali and condensation of the oxiran (XVIII) with amines.



We also tried to brominate 4-acetyl-4-phenyltetrahydropyran as an alternate route to the bromo ketone (XVI) but consistently obtained 4-dibromoacetyl-4-phenyltetrahydropyran (XIX). The structure of this compound was proved by degradation to 4-carboxy-4-phenyltetrahydropyran.[3]

Pharmacological Results

1-(4-Phenyl-4-tetrahydropyranyl-2-piperidino-ethanol and -2-dipropylaminoethanol have been tested by Dr. E. J. Fellows of Smith, Kline and French Laboratories. No analgetic activity was observed in rats at non-toxic dose levels. Topical anesthetic activity was absent or only very slight for 1% solutions and was accompanied by irritation. No significant protective activity against histamine-induced bronchospasm, nor anticonvulsant activity were observed at non-toxic doses. Both compounds produced coronary constriction in the iso-

(3) Eisleb, *Ber.*, **74**, 1433 (1941).

lated rabbit heart. The dipropylamino alcohol caused cardiac depression comparable to that of khellin.

Experimental[4]

4-Phenyl-4-tetrahydropyranoyl Chloride (XV).—Bis-(β-chloroethyl) ether was condensed with phenylacetonitrile in 62% yield under the influence of lithamide. The nitrile was hydrolyzed under ordinary pressure by refluxing for 11 hours with a 20% isoamyl alcoholic solution of potassium hydroxide. The yield of 4-phenyl-4-carboxytetrahydropyran of melting point 125.5–128.5° was 86.5%. The chloride was obtained according to Eisleb[3] in 66.5% yield; it boiled at 104–106° (1 mm.) and melted at 51–52°.

4-Phenyl-4-bromoacetyltetrahydropyran (XVI).—A solution of 70 g. (0.31 mole) of 4-phenyl-4-tetrahydropyranoyl chloride in 100 cc. of dry ether was added to a cooled dry solution of 33 g. (0.79 mole) of diazomethane in 1400 cc. of ether. The solution was allowed to stand overnight at room temperature, filtered to remove a slight flocculent precipitate and a solution of 37.5 cc. of 48.5% aqueous hydrobromic acid in 37.5 cc. of ether was dropped into the stirred solution. Stirring was continued for two hours after the addition was complete. The solution was neutralized with aqueous sodium carbonate, the ether layer dried over sodium sulfate and the solvent removed.

1-(4-Phenyl-4-tetrahydropyranyl)-2-bromoethanol (XVII).—The bromo ketone (XVI) was reduced by the Meerwein, Ponndorf and Verley method. When the bromohydrin (XVII) was treated with a cold 2.2% absolute ethanolic potassium hydroxide solution, and the reaction mixture was worked up, a colorless ether soluble oil containing no halogen was obtained and was presumably, 4-phenyl-4-oxiranyltetrahydropyran (XVIII). It was used without further purification in the condensation with morpholine.

1-(4-Phenyl-4-tetrahydropyranyl)-2-morpholinoethanol (V, NR_2 = NC_4H_8O).—A mixture of 4 g. (0.0196 mole) of 4-phenyl-4-oxiranyltetrahydropyran and 8.5 g. (0.098 mole) of morpholine was refluxed for nine hours, the excess morpholine was removed under reduced pressure and the dark oily residue dissolved in dry ether. When ethereal hydrogen chloride was added a crystalline hydrochloride precipitated. A mixture melting point with a sample obtained from the reduction of the morpholino ketone (method b) showed no depression.

4-Phenyl-4-dialkylaminoacetyltetrahydropyran Derivatives.—A solution of 0.1 mole of 4-phenyl-4-bromoacetyltetrahydropyran and 0.2 mole of secondary amine (diethylamine, morpholine, piperidine) in 200 cc. of dry ether was allowed to stand overnight, the mixture was washed with water, the ether solution was dried, concentrated and the residual amino ketone was converted to a crystalline salt.

β-(4-Phenyl-4-tetrahydropyranyl)-dialkylaminoethanol Derivatives.—In addition to the preparation of the morpholino alcohol from the oxiran described above the following methods have been used: (a) a solution of 0.1 mole of the bromohydrin (XVII) and 0.2 mole of the secondary amine in 500 cc. of dry benzene was refluxed for 48 hours, the precipitated amine hydrobromide was filtered and the amino alcohol extracted into dilute hydrochloric acid. It was recovered from the acid solution by alkalization, extraction and conversion to a crystalline salt.

(b) A solution of 0.04 mole of a 4-phenyldialkylaminoacetyltetrahydropyran (IV) in 200 cc. of isopropyl alcohol was reduced with aluminum isopropoxide for twelve hours and worked up as usual. The amino alcohol was purified, in one case, by distillation and otherwise by conversion to a crystalline salt. The hydrochlorides of the morpholino and piperidino alcohols obtained by this method gave no mixture melting point depression with the salts of the corresponding compounds obtained by treatment of the bromohydrin or oxiran derivative, respectively.

(4) All melting points have been corrected. Microanalyses by Clark Microanalytical Laboratory, Urbana, Illinois.

4-Phenyl-4-acetyltetrahydropyran (XIII).—A solution of 40 g. (0.214 mole) of 4-phenyl-4-cyanotetrahydropyran (XII) in 120 cc. of dry benzene was added over a period of thirty minutes to a benzene solution of 107 g. (0.642 mole) of methylmagnesium iodide, and the mixture was refluxed and stirred for 42 hours. It was then hydrolyzed with dilute hydrochloric acid and worked up as usual.

4-Phenyl-4-dibromoacetyltetrahydropyran (XIX).—This compound was obtained by bromination of the ketone (XIII) in ten volumes of carbon tetrachloride at room temperature. Hydrobromic acid was washed out with water and the solvent removed. The dibromo compound crystallized on standing.

Haloform Reaction.—Chlorine was passed into a stirred solution of 4 g. of 4-phenyl-4-dibromoacetyltetrahydropyran and 1.5 g. of potassium hydroxide in 20 cc. of methanol and 4 cc. of water. The temperature rose to 85°, and 25% aqueous potassium hydroxide was added until the volume reached 80 cc. The mixture was refluxed for three hours, filtered and acidified. 4-Phenyl-4-carboxytetrahydropyran crystallized slowly and melted, after recrystallization from water at 124.5–125.5°. A mixture melting point with an authentic sample showed no depression.

1-(4-Phenyl-4-tetrahydropyranyl)-ethylamine (III).—Forty-six grams (0.226 mole) of 4-phenyl-4-acetyltetrahydropyran was added to 71.2 g. (1.13 moles) of ammonium formate at 170° and the temperature was maintained for six hours. The amide was hydrolyzed by refluxing for ten hours with 116 cc. of 20% hydrochloric acid. The dark solution was extracted with benzene, cleared with Norite and the amine was liberated with alkali. The hydrochloride of the amine was prepared in ethanol–ether solution. The benzoyl derivative was obtained by the Schotten–Baumann method.

1-(4-Phenyl-4-tetrahydropyranyl)-N-methylethylamine (XIV) was prepared in a similar manner using methylammonium formate at 200° for 7.5 hours.

4-Tetrahydropyranylmethanol (VIII).—A solution of 77.5 g. (0.597 mole) of 4-carboxytetrahydropyran in 800 cc. of ether was added over a two-hour period to a solution of 45.7 g. (1.2 moles) of lithium aluminum hydride in 1250 cc. of ether. The mixture was refluxed an additional 90 minutes, cooled, hydrolyzed with dilute sulfuric acid and worked up. Fractionation of the residue yielded 23.4 g. of a colorless oil, b. p. 105–110° (20 mm.), $n^{28}D$ 1.460. The phenylurethan derivative melted at 86.5–88°.

Anal. Calcd. for $C_{12}H_{17}NO_3$: N, 5.95. Found: N, 5.90.

Twenty-nine grams of unreacted acid was recovered, and the yield of the carbinol, based on acid consumed in the reaction was 55%.

4-Bromomethyltetrahydropyran (IX).—A solution of 60 g. (0.518 mole) of 4-tetrahydropyranylmethanol in 550 cc. of dry chloroform was treated with 35 cc. of phosphorus tribromide at −10° at such a rate that the temperature did not exceed 0°. The mixture was allowed to stand at room temperature overnight, the chloroform was removed, the residual oil decomposed with ice, and extracted with ether. Thirty-two grams (34.6%) of a viscous oil distilled at 84–86° (20 mm.); $n^{28}D$ 1.4918. The β-naphthyl ether derivative consisted of colorless platelets, m. p. 70–72°.

Anal. Calcd. for $C_{16}H_{18}O_2$: C, 79.31; H, 7.49. Found: C, 79.35; H, 7.57.

α-Methyl-β-(4-tetrahydropyranyl)-propionic Acid (XI).—A solution of 30 g. (0.168 mole) of 4-bromomethyltetrahydropyran in 15 cc. of ethanol was added to a stirred solution of diethyl sodiomethylmalonate prepared from 32 g. (0.183 mole) of diethyl methylmalonate and 4.2 g. (0.183 mole) of sodium in 85 cc. of ethanol. The mixture was stirred and refluxed overnight, the precipitated sodium bromide was filtered, the solvent was removed, the residue taken up in water and extracted into ether. Fractionation of the oily residue furnished 30 g. (65.5%) of colorless ester, b. p. 134–137° (0.5 mm.). This ester was hydrolyzed by refluxing with a solution of 20.1 g. of potassium hydroxide in 42 cc. of water and 183 cc. of ethanol overnight; the alcohol was stripped off and the malonic

acid derivative was precipitated by acidification. The colorless crystalline material was dried and decarboxylated at 145°. The resulting propionic acid derivative was purified by distillation, b. p. 130–135° (0.5 mm.). The yield was 77%. The material crystallized on standing, m. p. 37–43°.

Anal. Calcd. for $C_9H_{16}O_3$: C, 62.76; H, 9.37. Found: C, 62.96; H, 9.28.

1-(4-Tetrahydropyranyl)-2-aminopropane (I).—α-Methyl-β-(4-tetrahydropyranyl)-propionyl chloride was obtained from the acid (XI) and excess thionyl chloride in a yield of 90%. The colorless liquid boiled at 85° (0.5 mm.). A solution of 12 g. (0.063 mole) of this acid chloride in 30 cc. of dry xylene was added slowly to a stirred mixture of 20 g. of (technical) sodium azide and 120 cc. of heated xylene. The calculated amount of nitrogen was evolved within two hours. Inorganic salts were filtered, and the clear xylene solution was refluxed with 135 cc. of 12 *N* hydrochloric acid for three hours. The acid layer was separated, made alkaline with sodium hydroxide and the precipitated oil was extracted into ether. A yield of 7.3 g. (81%) of a clear colorless liquid, b. p. 89° (20 mm.), was obtained. The base was converted to the colorless hydrochloride in ether solution, and the salt was recrystallized from methanol–ethyl acetate.

Anal. Calcd. for $C_8H_{17}NO\cdot HCl$: C, 53.45; H, 10.10; N, 7.80. Found: C, 53.63; H, 10.15; N, 7.98.

Summary

1. 1-(4-Tetrahydropyranyl)-2-aminopropane was synthesized in seven steps from 4-carboxytetrahydropyran, and 1-(4-phenyl-4-tetrahydropyranyl)-ethylamine from 4-acetyl-4-phenyltetrahydropyran.

2. A number of derivatives of 1-(4-phenyltetrahydropyranyl)-2-dialkylaminoethanol were prepared from 4-phenyl-4-carboxytetrahydropyran by way of 4-phenyl-4-bromoacetyltetrahydropyran through the corresponding bromohydrin or the corresponding amino ketones.

CHARLOTTESVILLE, VIRGINIA RECEIVED MAY 20, 1950

[CONTRIBUTION FROM HAVEMEYER LABORATORY, COLUMBIA UNIVERSITY]

The Peracetic Acid Cleavage of Unsymmetrical Ketones[1]

BY W. VON E. DOERING AND LOUISE SPEERS

Since Baeyer and Villiger[2] first discovered that Caro's acid would cleave menthone, tetrahydrocarvone and camphor to related lactones, numerous carbonyl compounds have been treated with Caro's acid or with the related reagents, peracetic and perbenzoic acid, to obtain the appropriate ester or lactone. Among alicyclic compounds may be mentioned cyclohexanone,[3] suberone,[4] C_{13}–C_{17} ring ketones,[5] 3-ketosteroid derivatives,[6,7,8,9] 17-ketosteroids,[10] sarsasapogenin,[11] 20-ketopregnanes[12,13,14] and, surprisingly, α,β-unsaturated ketones, which are cleaved to enol esters.[15] A few aliphatic–aromatic ketones, *p*-methoxyacetophenone,[16] and, very recently, acetophenone, propiophenone and β-acetonaphthone,[17] have been cleaved as have four aromatic ketones, benzophenone,[18] Michler's ketone,[19] *p*-nitrobenzophenone[19] and fluorenone.[20]

The behavior of the unsymmetrical ketones in the literature permits the generalization that 2°[2,11,12,13,14] and 3°[10,21] alkyl groups migrate to oxygen more readily than 1° groups. Theoretically related is the fact that the remarkable peracetic acid oxidations of benzaldehydes to phenylformates[16] proceed only when a hydroxyl or amino group is in the ortho or para position. From these few facts the hypothesis is suggested that groups which bear positive charge more readily (as judged from other reactions) will rearrange more rapidly in the peracid cleavage. As a further test of this hypothesis, the behavior of substituted benzophenones has been investigated.

In Table I, which contains the pertinent results as well as most of the experimental details, the penultimate column shows that *p*-anisyl (expts. 8–10) and *p*-tolyl (expt. 11) migrate more rapidly than phenyl whereas *p*-chlorophenyl (expts. 14–17), *p*-bromophenyl (expt. 19), *p*-nitrophenyl[19] (expts. 20–22) and *p*-anilinium (expt. 27) migrate less rapidly than phenyl. In the absence of sulfuric acid (expts. 14 and 18) *p*-chloro- and *p*-bromobenzophenone react inexplicably to a slight

(1) This work is taken from a dissertation submitted January 21, 1949, in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Faculty of Pure Science of Columbia University.

(2) Baeyer and Villiger, *Ber.*, **32**, 3625 (1899).

(3) Stoll and Schemer, *Helv. Chim. Acta*, **13**, 142 (1930).

(4) Baeyer and Villiger, *Ber.*, **33**, 858 (1900).

(5) Ruzicka and Stoll, *Helv. Chim. Acta*, **11**, 1159 (1928).

(6) Windaus, *Ber.*, **37**, 2027 (1904).

(7) Gardner and Godden, *Biochem. J.*, **7**, 588 (1913).

(8) Burckhardt and Reichstein, *Helv. Chim. Acta*, **25**, 821, 1434 (1942).

(9) Prelog, Ruzicka, Meister and Wieland, *ibid.*, **28**, 618 (1945); Ruzicka, Prelog and Meister, *ibid.*, **28**, 1651 (1945).

(10) (a) Jacobsen, *J. Biol. Chem.*, **171**, 61 (1947); (b) Levy and Jacobsen, *ibid.*, **171**, 71 (1947); (c) Jacobsen, Picha and Levy, *ibid.*, **171**, 81 (1947).

(11) Marker, Rohrmann, Crooks, Wittle, Jones and Turner, THIS JOURNAL, **62**, 525 (1940).

(12) Marker, *et al.*, *ibid.*, **62**, 650, 2543, 3003 (1940).

(13) Marker, *ibid.*, **62**, 2621 (1940).

(14) Sarett, *ibid.*, **69**, 2899 (1947).

(15) Böeseken and Kremer, *Rec. trav. chim.*, **50**, 827 (1931); Böeseken and Soesman, *ibid.*, **52**, 874 (1933); Böeseken and Jacobs, *ibid.*, **55**, 786 (1936).

(16) Wacek and Bézard, *Ber.*, **74**, 845 (1941).

(17) Friess, THIS JOURNAL, **71**, 14 (1949).

(18) Dilthey, Inckel and Stephan, *J. prakt. Chem.*, **154**, 219 (1939).

(19) Dilthey, Quint and Dierichs, *ibid.*, **151**, 25 (1938).

(20) Wittig and Pieper, *Ber.*, **73**, 295 (1940).

(21) The opposite behavior of camphor[2] in giving campholide may be attributed to the fact that the 3° substituent is part of a bridgehead.