Compounds II–VI were prepared by the following general procedure. The tetracycline was added to a stirred mixture of the alcohol and aldehyde, and the mixture refluxed to give a clear solution. The time in each case was determined by a preliminary small-scale reaction, followed closely by paper chromatography. The solution was allowed to cool, then taken to dryness *in vacuo*, and worked up with anhydrous ether to a solid. Analytical samples were obtained by dissolving the crude solid in chloroform, then washing several times with water. The chloroform, after drying (Na_2SO_4), was evaporated *in vacuo*, and the residue was worked up with anhydrous ether to yield the appropriate alkoxyalkyltetracycline.

N-(1-Methoxy)ethyltetracycline (II).—Tetracycline (4.44 g., 0.01 mole), methanol (75 ml.), and acetaldehyde (25 ml.) were refluxed 2.5 hr. A portion (85%) of the cooled solution, when worked up, gave 1.5 g. of crude II. From the crude material there was obtained 400 mg. of analytically pure II: $\lambda_{max}^{0.1\ N\ HCl}$ 218 mμ (ε 14,800), 270 (19,100), and 360 (12,100).

Anal. Calcd. for $C_{25}H_{30}N_2O_9$: C, 59.75; H, 6.02; N, 5.57. Found: C, 59.64; H, 5.99; N, 5.04, 5.32.

N-(1-Methoxy)propyltetracycline (III).—A mixture of tetracycline (8.88 g., 0.02 mole), methanol (150 ml.), and propionaldehyde (50 ml.) was refluxed 2.5 hr. to give 3.65 g. of crude III. From 2.4 g. of crude material 250 mg. of analytically pure III was obtained: $\lambda_{max}^{0.1\ N\ HCl}$ 218 mμ (ε 15,600), 270 (19,100), and 360 (13,900).

Anal. Calcd. for $C_{26}H_{32}N_2O_9$: C, 60.45; H, 6.25; N, 5.42. Found: C, 59.70; H, 6.39; N, 5.65.

N-(1-Methoxy)methylchlorotetracycline (IV).—A mixture of chlorotetracycline (24.0 g., 0.05 mole), methanol (300 ml.), and a 46.5% solution of formaldehyde in methanol[6] (100 ml.) was refluxed 45 min. Work-up gave 19.3 g. of crude material. From 3.0 g. of crude material, 900 mg. of analytically pure IV was obtained: $\lambda_{max}^{0.1\ N\ HCl}$ 230 mμ (ε 17,200), 268 (18,000), and 370 (9140).

Anal. Calcd. for $C_{24}H_{27}ClN_2O_9$: C, 55.12; H, 5.20; Cl, 6.78; N, 5.36. Found: C, 54.85; H, 5.27; Cl, 7.09; N, 5.27.

N-(1-Methoxy)ethylchlorotetracycline (V).—A mixture of chlorotetracycline (7.2 g., 0.015 mole), methanol (30 ml.), and acetaldehyde (15 ml.) was refluxed for 2.75 hr. Work-up gave 5.47 g. of crude material. From 2.0 g. of crude product, 820 mg. of analytically pure V was obtained: $\lambda_{max}^{0.1\ N\ HCl}$ 230 mμ (ε 17,700), 268 (18,200), and 370 (10,200).

Anal. Calcd. for $C_{25}H_{29}ClN_2O_9$: C, 55.92; H, 5.44; Cl, 6.60; N, 5.22. Found: C, 55.44; H, 5.22; Cl, 6.52; N, 5.22.

N-(1-Methoxy)propylchlorotetracycline (VI).—A mixture of chlorotetracycline (9.6 g., 0.02 mole), methanol (120 ml.), and propionaldehyde (40 ml.) was refluxed 1.5 hr. Work-up yielded 9.7 g. of crude material. From 2.0 g. of crude material there was obtained 850 mg. of analytically pure VI: $\lambda_{max}^{0.1\ N\ HCl}$ 230 mμ (ε 17,600), 266 (18,150), and 370 (10,200).

Anal. Calcd. for $C_{26}H_{31}ClN_2O_9$: C, 56.67; H, 5.67; Cl, 6.44; N, 5.08. Found: C, 56.50; H, 5.81; Cl, 6.50; N, 5.20.

N-(1-Methoxy)methylchlorotetracycline (IV) Ethylenediamine Salt.—To IV (500 mg., 0.96 mmole) was added 14 ml. of a 10% water-in-methanol solution. Triethylamine (0.28 ml.) was added and the solution warmed to 50°. Next 2.0 ml. of an ethylenediamine-in-methanol solution (prepared by adding 1.6 ml. of ethylenediamine to 14.4 ml. of MeOH) was added, and after several minutes of stirring the crystalline salt appeared. After cooling and filtering, the crystals were washed with a 10% water-in-methanol solution, then anhydrous ether, and dried.

Anal. Calcd. for $C_{26}H_{35}ClN_4O_9$: C, 53.56; H, 6.05; Cl, 6.08; N, 9.61. Found: C, 53.20; H, 6.33; Cl, 6.19, 6.23; N, 9.59.

N-(1-Methoxy)ethylchlorotetracycline (V) Ethylenediamine Salt.—Treatment of V, as above, gave the crystalline ethylenediamine salt of V.

Anal. Calcd. for $C_{27}H_{37}ClN_4O_9$: C, 54.31; H, 6.25; Cl, 5.94; N, 9.38. Found: C, 53.95; H, 5.75; Cl, 6.02; N, 9.24.

I and Methanesulfonyl Chloride.—A solution of I (1 g., 1.9 mmoles) in pyridine (10 ml.) was cooled to 0°. To this was slowly added methanesulfonyl chloride (0.3 ml.) while the temperature was kept below 5°. The mixture was stirred 1 hr. at 0–5° and filtered. The filtrate was precipitated into anhydrous ether (40 ml.). The gummy solid obtained was washed several times with anhydrous ether, then worked up by stirring with acetone. A solid was obtained which was shown to be mainly I and some tetracycline. The infrared spectrum showed no nitrile absorption at 4.53 μ.

Under identical conditions, tetracycline was dehydrated at the carboxamide to give tetracycline nitrile as the major product,[7] as demonstrated by paper chromatography and infrared spectrum (absorption at 4.53 μ).

Various Alkoxyalkylation Attempts Followed by Paper Chromatography.—Reactions of tetracyclines with other alcohols and aldehydes were carried out as previously described for I–VI. These were followed by paper chromatography,[3] and in most cases new components were detected on chromatograms. These reaction products were not characterized, but are believed to be alkoxyalkyltetracyclines analogous to I–VI. Those reactions which produced new compounds as demonstrated by paper chromatography are summarized.

Tetracycline and formaldehyde reacted with the following alcohols: ethanol, *n*-butyl alcohol, *t*-butyl alcohol, benzyl alcohol, α-hydroxyacetic acid, 2-phenylethanol, lactic acid, sorbitol, and mannitol. Tetracycline and methanol reacted with the following aldehydes: glyoxylic acid, 2-pyridinealdehyde, *p*-nitrobenzaldehyde, *p*-chlorobenzaldehyde, 2-furfural, and chloroacetaldehyde. Similarly 6-demethyltetracycline and methanol reacted with formaldehyde and propionaldehyde.

Acknowledgment.—The authors are indebted to Mr. L. Brancone, Mr. W. Fulmor, Mr. A. Dornbush, and Mr. G. Redin and their associates for the microanalyses, ultraviolet analyses, microbiological assays, and biological testing, respectively.

(7) J. R. D. McCormick, S. M. Fox, L. L. Smith, B. A. Bitler, J. Reichenthal, V. E. Origoni, W. H. Muller, R. Winterbottom, and A. P. Doerschuk, *J. Am. Chem. Soc.*, **79**, 2849 (1957).

Synthesis of Heterocyclic-Substituted Chromones and Related Compounds as Potential Anticancer Agents[1]

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In continuing previous studies[3] in this laboratory on the synthesis of potential anticancer agents, a further series of heterocyclic-substituted chromones and related compounds has been prepared and submitted for screening under the auspices of the Cancer Chemotherapy National Service Center.

The chromones were synthesized by a standard three-step procedure involving (1) condensation of the appropriate 2-hydroxyacetophenones with heterocyclic acid chlorides to form the esters listed in Table I, (2) Baker–Venkataraman rearrangement[4] of these esters to the corresponding 1,3-diketones listed in Table II, and (3) dehydrative cyclization of the diketones to the corresponding chromones shown in Table III. The diketone, 1-(2-hydroxy-5-methoxyphenyl)-3-(2-quinolyl)propane-1,3-dione, was not isolated in the pure state; Baker–Venkataraman rearrangement of the corresponding ester (II) gave an inseparable mixture of red and white products (pre-

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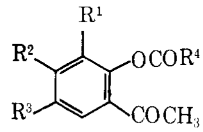
(2) Deceased.

(3) P. F. Devitt, A. Timoney, and M. A. Vickars, *J. Org. Chem.*, **26**, 4941 (1961).

(4) W. Baker, *J. Chem. Soc.*, 1381 (1933); H. S. Mahal and K. Venkataraman, *Current Sci.* (India), **2**, 214 (1933); B. G. Doyle, F. Gogan, J. E. Gowan, J. Keane, and T. S. Wheeler, *Sci. Proc. Roy. Dublin Soc.*, **24**, 291 (1948).

TABLE I

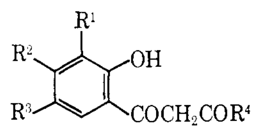
2-ACYLOXYACETOPHENONES



No.	R^1	R^2	R^3	R^4	M.p., °C.	Yield, %	Formula	Calcd., % C	H	Cl	N	Found, % C	H	Cl	N
I	OCH_3	OCH_3	H	2-Quinolyl	130	30	$C_{20}H_{17}NO_5$	68.4	4.9	...	4.0	68.7	4.7	...	4.0
II	H	H	OCH_3	2-Quinolyl	176–177	40	$C_{19}H_{15}NO_4$	71.0	4.7	...	4.4	71.1	4.9	...	4.5
III	H	H	Cl	2-Quinolyl	183–184	56	$C_{18}H_{12}ClNO_3$	66.4	3.7	10.9	...	66.2	3.8	10.8	...
IV	H	H	Cl	2-Pyridyl	128–129	50	$C_{14}H_{10}ClNO_3$	61.0	3.7	12.9	...	61.2	3.7	12.9	...
V	H	H	Cl	3-Pyridyl	75–76	57	$C_{14}H_{10}ClNO_3$	61.0	3.7	12.9	...	61.0	3.7	13.2	...
VI	H	H	Cl	2-Furyl	82–83	89	$C_{13}H_9ClO_4$	59.0	3.4	13.4	...	59.0	3.5	13.9	...
VII	H	H	Cl	2-Thienyl	80–82	89	$C_{13}H_9ClO_3S$	55.6	3.2	12.6	...	55.5	3.4	11.6	...

TABLE II

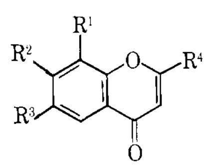
PROPANE-1,3-DIONES



No.	R^1	R^2	R^3	R^4	M.p., °C.	Yield, %	Formula	Calcd., % C	H	Cl	N	Found, % C	H	Cl	N
VIII	OCH_3	OCH_3	H	2-Quinolyl	123–124	60	$C_{20}H_{17}NO_5$	68.4	4.9	...	4.0	68.5	5.0	...	4.2
IX	H	H	Cl	2-Quinolyl	160–162	54	$C_{18}H_{12}ClNO_3$	66.4	3.7	10.9	4.3	66.3	3.7	10.5	4.2
X	H	H	Cl	3-Pyridyl	184–185	70	$C_{14}H_{10}ClNO_3$	61.0	3.7	12.9	5.1	60.6	3.8	12.3	5.2
XI	H	H	Cl	2-Furyl	116–117	80	$C_{13}H_9ClO_4$	59.0	3.4	13.4	...	58.8	3.3	13.4	...
XII	H	H	Cl	2-Thienyl	104–105	92	$C_{13}H_9ClO_3S$	55.6	3.2	12.6	...	55.7	2.9	12.8	...

TABLE III

CHROMONES[a]

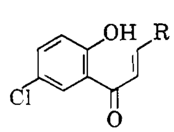


No.	R^1	R^2	R^3	R^4	M.p., °C.	Yield, %	Formula	Calcd., % C	H	Cl	N	Found, % C	H	Cl	N
XIII	OCH_3	OCH_3	H	2-Quinolyl	214–215	72	$C_{20}H_{15}NO_4$	72.1	4.5	...	4.2	71.9	4.5	...	3.9
XIV	H	H	OCH_3	2-Quinolyl	207–208	29	$C_{19}H_{13}NO_3$	75.2	4.3	...	4.6	75.5	4.4	...	5.4
XV	H	H	Cl	2-Quinolyl	232–233	80	$C_{18}H_{10}ClNO_2$	70.3	3.3	...	4.6	70.6	3.3	...	4.7
XVI[b]	H	H	Cl	3-Pyridyl	197–198	91	$C_{14}H_8ClNO_2$	65.2	3.1	13.8	...	64.8	3.2	13.9	...
XVII	H	H	Cl	2-Furyl	210	87	$C_{13}H_7ClO_3$	63.3	2.9	14.4	...	63.4	3.0	13.7	...
XVIII	H	H	Cl	2-Thienyl	174–175	92	$C_{13}H_7ClO_2S$	59.4	2.7	13.5	...	59.8	2.8	13.4	...

[a] All chromones, except XVI, are new compounds. [b] This compound, prepared by a different method, was reported[6] with m.p. 187–188°.

sumably diketone and chromone) which was cyclized directly to the chromone XIV.

The related 2-hydroxyacrylophenones (XIX–XXIV)[5-7] were obtained from alkali-catalyzed con-



XIX, R = 2-quinolyl
XX, R = 2-pyridyl
XXI, R = 3-pyridyl
XXII, R = 4-pyridyl
XXIII, R = 2-furyl
XXIV, R = 2-thienyl

densation of the appropriate heterocyclic aldehydes with 5-chloro-2-hydroxyacetophenone.

(5) R. Kuhn and H. R. Hensel, *Chem. Ber.*, **86**, 1333 (1953).
(6) A. C. Annigeri and S. Siddappa, *Indian J. Chem.*, **2**, 413 (1964).
(7) P. L. Cheng, P. Fournari, and J. Tirouflet, *Bull. soc. chim. France*, 2248 (1963).

Of chief interest among the compounds tested for anticancer activity in the earlier series,[3] and so far in the present one, is 6-chloro-2-(2-quinolyl)chromone (XV). This displayed borderline, though significant, activity against Sarcoma 180 in all trials. No comparable degree of activity was shown by the other 2-(2-quinolyl)chromones (XIII and XIV) and this finding tempted us to correlate the activity of the compound with the presence of the chlorine atom in the molecule. Accordingly, we were interested in preparing the other chlorinated derivatives. The screening data available on these compounds are preliminary and, as with XV, both toxicity and antitumor activity varied unpredictably from test to test. Though final assessment awaits further testing, the preliminary results in many cases show a degree of reduction in tumor weight which suggests that there may be a

TABLE IV

ANTITUMOR ACTIVITY OF HETEROCYCLIC SUBSTITUTED CHROMONES AND RELATED COMPOUNDS[a]

Compd.	Test[b] system	Dose, mg./kg.	Survivors	Animal wt. dif., g. (T − C)[c]	Tumor wt., mg. (T/C)	% T/C	Cell culture ED50[d]	Cell culture Slope[e]
VIII	SA	375	5/6	−0.7	645/1091	59		
	CA	300	8/10	−2.4	1141/1723	66		
IX	SA	300	6/6	−1.9	1115/1377	80	13	−0.60
	CA	270	10/10	−0.6	590/848	69		
		270	9/10	−1.8	154/1056	14		
X	SA	250	5/6	−4.4	402/978	41	24	0.95
		250	5/6	−7.6	190/293	64		
	CA	200	10/10	−4.9	781/1236	63		
XI	SA	250	0/6	...	...	Toxic	>10	...
		62	6/6	−0.3	1688/1820	92		
	CA	50	10/10	−1.0	1275/1849	68		
XII	SA	250	0/6		...	Toxic	4.7	−0.73
		62	2/6	−0.8	1313/1820	Toxic		
		31	0/6	...	...	Toxic		
XIII	SA	125	5/6	−1.0	834/1091	76		
	CA	100	10/10	−1.0	1654/1723	95		
XIV	SA	250	5/6	−0.3	588/753	74		
	CA	250	9/10	0.2	792/1171	67		
XV	SA	300	2/6	−8.0	162/1377	Toxic	49	−0.71
		150	6/6	−5.5	300/1342	22		
		150	6/7	−2.7	359/1371	26		
		150	3/6	−1.3	305/1434	Toxic		
		150	6/7	−2.6	435/1105	39		
		150	5/6	−2.6	444/793	55		
		150	2/7	−5.8	527/1277	Toxic		
		150	2/6	−4.2	202/1298	Toxic		
		115	1/7	−2.9	175/755	Toxic		
		115	6/7	−0.8	435/706	61		
		85	4/7	−0.8	535/1067	Toxic		
		85	4/7	−3.0	598/1583	Toxic		
		63	4/6	−0.7	813/1470	55		
	CA	44	9/10	−2.2	751/792	94		
XVI	SA	125	6/6	−4.5	817/978	83	>100	...
	CA	100	10/10	−2.1	547/1236	44		
		100	10/10	−1.2	706/1037	68		
XVII	SA	125	6/6	0.8	1477/1288	114	>10	...
	CA	100	10/10	1.4	1298/1378	94		
XVIII	SA	125	4/6	1.0	936/1393	67	>10	...
	CA	90	10/10	1.7	595/1378	43		
		90	10/10	−1.1	1698/1849	91		
XIX	SA	250	0/6	...	...	Toxic	7.9	0.55
		62	6/6	−1.0	975/1106	88		
XXI	SA	250	0/6	...	...	Toxic	14	0.70
		125	5/6	−2.4	227/676	40		
		125	6/6	−1.9	1207/1304	92		
	LL	87	6/6	−4.1	595/1042	57		
XXII	SA	250	0/7	...	.	Toxic	27	−1.1
		65	7/7	−2.9	725/1396	51		
		65	6/7	−3.1	650/1209	53		
	LL	45	5/6	−5.1	440/1120	39		
		45	6/6	−2.8	485/796	60		
XXIII	SA	250	6/6	−2.3	813/748	108	6.2	0.39
XXIV	SA	250	6/6	−1.1	655/748	87	3.5	−0.87
							8.3	2.70

[a] For testing procedures see *Cancer Chemotherapy Rept.*, **25,** 1 (1962). [b] SA = Sarcoma 180, CA = Adenocarcinoma 755, LL = Lewis lung carcinoma. [c] T = test animal, C = control animal. [d] ED_{50} = dose (γ/ml.) that inhibits growth to 50% of control growth. [e] Slope = difference in response for a tenfold difference in dose.

relationship between the chloro-2-hydroxyphenyl-C–C–C-heterocycle (furyl excepted) type of structure and anticancer activity against the sarcoma and carcinoma systems which might be worthy of further investigation. No extension of this study can be carried out by us in the immediate future.

The screening data of interest are summarized in Table IV. None of the esters tested (IV–VII) were active against any of the usual systems and all of the compounds tested were inactive against lymphatic leukemia L1210. The acrylophenones, XIX, XXIII, and XXIV, were inactive against Friend virus leukemia (solid form). These results are not included in Table IV. Some of the compounds were also assayed for activity against the KB cell line in tissue cultures but none showed any reproducible activity of interest (*i.e.*, $ED_{50} \leq 4$ γ/ml.). These results are included in Table IV for comparison.

Experimental Section[8]

The preparation of the individual compounds listed below illustrates the general procedure for each class of compounds.

2-Acyloxyacetophenones (Table I). 5-Chloro-2-(2-quinolinecarboxy)acetophenone (III).—Quinaldoyl chloride (10.0 g., 0.052 mole) in dry benzene (80 ml.) was added gradually to a well-stirred ice-cold solution of 5-chloro-2-hydroxyacetophenone (8.9 g., 0.052 mole) in pyridine (70 ml.). After 24 hr. the mixture was added to excess dilute acetic acid. The product, which separated, crystallized from ethanol–acetone in needles. Melting points, per cent yields, and analyses are summarized in Table I. In the preparation of the esters IV–VII, the acid chloride was added dropwise to the pyridine solution of the acetophenone.

1-(2-Hydroxyphenyl)propane-1,3-diones (Table II). 1-(5-Chloro-2-hydroxyphenyl)-3-(2-quinolyl)propane-1,3-dione (IX).—Powdered KOH (2.5 g.) was added to a solution of 5-chloro-2-(2-quinolinecarboxy)acetophenone (5.0 g.) in dry pyridine (100 ml.). The mixture was shaken vigorously for 20 min. and set aside for 12 hr. The crude product, liberated by the addition of cold dilute acetic acid, was washed with water. It crystallized from ethanol–acetone in yellow needles. Melting points, etc., are recorded in Table II.

Chromones (Table III). 6-Chloro-2-(2-quinolyl)chromone (XV).—1-(5-Chloro-2-hydroxyphenyl)-3-(2-quinolyl)propane-1,3-dione (3.6 g.) in acetic acid (40 ml.) and H_2SO_4 (1 ml.) was heated on a steam bath for 15 min., poured onto crushed ice, and neutralized with 10% NaOH. The product which separated crystallized from ethanol–acetone in needles. Melting points, etc., are recorded in Table III.

Acrylophenones. 5-Chloro-2-hydroxy-3-(4-pyridyl)acrylophenone (XXII).—Aqueous KOH (50%, 10 ml.) was added to a solution of 5-chloro-2-hydroxyacetophenone (3.4 g., 0.02 mole) and pyridine-4-aldehyde (2.1 g., 0.02 mole) in ethanol (50 ml.). After being stirred at room temperature for 12 hr., the solution was neutralized with dilute acetic acid. The product, which separated, crystallized from alcohol in yellow needles, m.p. 143–144°, yield 40%.

Anal. Calcd. for $C_{14}H_{10}ClNO_2$: C, 64.7; H, 3.9; N, 5.4. Found: C, 64.5; H, 4.0; N, 5.5.

(8) Microanalyses were carried out by Mrs. E. M. Carey of the Department of Chemistry, University College, Dublin, and by Drs. Weiler and Strauss, Analytical Laboratory, Oxford, England.

Synthetic Spasmolytic Amines

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A study of some isomeric hexyl- and heptylamines by Marsh, *et al.*,[2] indicated that N-methyl substitution of these primary amines enhanced spasmolytic action and increased muscle relaxant activity while having no effect on the pressor activity of the amine. One of the more potent spasmolytic amines is 2-(3-methylbutyl)-amino 6-methylheptane (Octinum-D).[3] A more recent study[4] of N-alkyl-1,5-dimethylhexylamines has shown that these compounds exhibit some activity against acetylcholine-induced spasms and against blood pressure lowering.

The pharmacodynamic action of these amines has been conveniently compared with that of the natural alkaloids, atropine and papaverine, in their ability to prevent spasms of isolated muscle when activated by acetylcholine or barium chloride solutions, respectively. More often than not, these amines possess both actions. The rather interesting pressor activity data of simple amines and the properties of such a compound as 2-(3-methylbutyl)amino-6-methylheptane[5] prompted the synthesis of the compounds listed in Table I.

The secondary and tertiary amines were conveniently prepared by alkylating amines such as pyrrolidine, piperidine, morpholine, furfurylamine, and 2-aminomethyl-1,4-benzodioxane with the appropriate alkyl bromides, *e.g.*, isoamyl bromide 2-bromo-6-methylheptane, and 2-bromo-6-methylhept-5-ene.

The preparation of alkyl bromides was achieved by the reduction of the corresponding methyl ketone with potassium borohydride to give the secondary alcohol. Subsequent bromination of the alcohol with phosphorus tribromide gave the bromide.

The spasmolytic activity on isolated muscle tissue of the most active amines is listed in Table II. None of the amines tested were superior to either atropine or papaverine in spasmolytic activity.

Experimental Section[6]

Reduction of 6-Methylhept-5-en-2-one.—A solution of 16.2 g. (0.3 mole) of KBH_4 in 100 ml. of water[7] was added dropwise to a solution of 100 g. (0.8 mole) of 6-methylhept-5-en-2-one[8] in 200 ml. of methanol. The addition was made slowly to keep the temperature below 40°. After all the borohydride solution was added, the mixture was heated on a steam bath for 2 hr. and then cooled in an ice bath. A 1:1 solution of concentrated HCl and water (250 ml.) was then added to the reaction and the mixture was allowed to separate. The aqueous layer was extracted with three 100-ml. portions of ether and the combined organic layers were dried (Na_2CO_3). Distillation of the combined organic layers yielded 80 g. of 6-methylhept-5-en-2-ol, b.p. 76–78° (11 mm.).

Anal. Calcd. for $C_8H_{16}O$: C, 74.94; H, 12.58. Found: C, 75.11, 74.89; H, 12.74, 12.48.

Reduction of 6-Methylheptan-2-one.—A similar procedure as that described above gave 75% of 6-methylheptan-3-ol, b.p. 74° (15 mm.).

Anal. Calcd. for $C_8H_{18}O$: C, 73.78; H, 13.99. Found: C, 74.04, 74.38; H, 14.21, 14.51.

Bromination of 6-Methylhept-5-en-2-ol.—A mixture of 117 g. (0.91 mole) of 6-methylhept-5-en-2-ol and 35 g. (0.44 mole) of dry pyridine was cooled to −40° and kept at that temperature as 147 g. (0.52 mole) of PBr_3 was added dropwise over a period of 3 hr. The mixture was allowed to stand overnight at room temperature and then distilled under reduced pressure. A fraction boiling at 66–85° (17 mm.) was washed with cold saturated $NaHCO_3$ solution and extracted with 200 ml. of ether. The extract was dried (Na_2SO_4) and distilled to yield 134 g. of 2-bromo-6-methylhept-5-ene, b.p. 85–86° (27 mm.), $n^{20}D$ 1.4922.

Anal. Calcd. for $C_8H_{15}Br$: C, 50.27; H, 7.91; Br, 41.81. Found: C, 50.84; H, 8.12; Br, 41.36.

Bromination of 6-methylheptan-2-ol.—Phosphorus tribromide (380 g., 1.40 moles) was added over a period of 3 hr. to 177 g.

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(2) D. F. Marsh, A. Howard, and D. A. Herring, *J. Pharmacol. Exptl. Therap.*, **103**, 325 (1951).

(3) H. Hass, *Arch. Exptl. Pathol. Pharmakol.*, **227**, 71 (1955).

(4) (a) Y. Ota, G. Otani, and R. Enomoto, *Yakugaku Zasshi.*, **80**, 1153 (1960); (b) Y. Ota, *ibid.*, **81**, 403 (1961).

(5) (a) J. Paris and J. Vanlerenberghe, *Compt. rend. soc. biol.*, **146**, 265 (1950); (b) E. Savini, *Arch intern. pharmacodyn.*, **82**, 127 (1950).

(6) Melting points were taken in a mineral oil bath with an open capillary and are corrected. The authors are indebted to Mr. Sidney Alpert and his associates of the Analytical section for carrying out the nitrogen (Dumas method) analyses.

(7) Potassium borohydride solution was stabilized by the addition of a few drops of 1 *N* NaOH solution.

(8) Obtained from Givaudan-Delawanna, Inc., Phila., Pa., as methylheptenone.