Production of Penta-acetyl-*l*-acacatechin from *l*-Leucomaclurin-glycol Ether.—A solution of 5 g. of *l*-leucomaclurin-glycol ether in an excess of acetic anhydride is heated for forty minutes and the cold solution poured into water. The white solid formed on standing melts in the crude state at 149–151° and is practically pure penta-acetyl-*l*-acacatechin, which crystallizes from alcohol in needles melting at 151°. This melting point is not depressed when penta-acetyl-*l*-acacatechin from *l*-leucomaclurin-glycol ether is mixed in varying proportions with the penta-acetyl derivative of *l*-acacatechin from the heart-wood of *Acacia Catechu*, Willd. The rotation of penta-acetyl-*l*-acacatechin from *l*-maclurin-glycol ether in tetrachloro-ethane is $[\alpha]_D^{21}$ −12.0°, whereas penta-acetyl-*l*-acacatechin from *l*-acacatechin rotates in the same solvent $[\alpha]_D^{20}$ −11.5°, the same concentration being used in both cases.

Anal. Subs., 5.222, 4.642 mg.: CO_2, 11.376, 10.171; H_2O, 2.397, 2.084 mg. Calcd. for $C_{25}H_{24}O_{11}$: C, 60.00; H, 4.80. Found: C, 59.41, 59.76; H, 5.14, 5.02.

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Summary

It is shown that the young twigs of *Acacia Catechu*, Willd. contain *l*-leucomaclurin-glycol ether, which on acetylation yields penta-acetyl-*l*-acacatechin, the acetyl derivative of the catechin present in the heart-wood of this tree.

BRISTOL, ENGLAND

[CONTRIBUTION FROM THE ABBOTT LABORATORIES]

5,5-SUBSTITUTED BARBITURIC ACIDS[1]

BY E. H. VOLWILER AND D. L. TABERN

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Of the many types of chemical compounds which can produce sleep, the derivatives of barbituric acid continue to be by far the most important. During recent years, the availability of new alcohols has made possible the more systematic study of the homologs of the parent member of the series, barbital (diethylbarbituric acid), with the result that several new hypnotics of superior therapeutic merit have become available. More than a hundred barbituric acid derivatives have been synthesized and most of them have been pharmacologically tested; a number of them have found their way into clinical use.

Considerable variation in sleep-producing activity exists among the members of this series, ranging from none at all to over four times that of barbital. If this increase in efficiency over barbital were merely accompanied by a corresponding increase in toxicity, there would be little attained by the study of the newer barbituric acid derivatives. This is not neces-

[1] Presented before the Medicinal Products Division of the American Chemical Society at Minneapolis, Sept. 10, 1929.

sarily the case, however, for experiments on animals have shown that sleep-producing efficiency and other pharmacological properties may not vary to the same degree as toxicity. This is to be expected, for solubilities, rates of absorption and elimination, etc., would be likely to be different for various members of the series. These observations are also of interest in connection with the intravenous use of certain barbiturates for the production of general anesthesia.

From the study of scores of these new barbituric acid derivatives, it has been possible to arrive at some conclusions regarding the pharmacologic effects of lengthening the saturated hydrocarbon radicals on the carbon atom in the 5-position,[2] the influence of unsaturation in these radicals[3] and the effect of substitution on the nitrogen of the barbituric acid nucleus.[4] Also, the results produced by other modifications have been studied, such as the substitution of cyclic structures, halogens, ether groups, amino radicals, etc.

Up to the present time, the study of the effects of alkyl groups has been limited largely to homologs, and comparatively little attention has been given to the results produced by isomerism of the alkyl groups. This is due to the fact that until recently few isomeric alcohols beyond the butyl series have been available. In the latter series, the normal, iso and secondary butyl radicals have been introduced into barbituric acid and the pharmacologic effects carefully observed; attempts to prepare tertiary butyl substituted barbituric acids have failed.

The present availability of isomeric amyl alcohols has made possible a somewhat more extended comparative study of the effects of isomerism on hypnotic action. In addition to the normal and iso-amyl alcohols, the following alcohols are now commercially available: 1-methylbutyl alcohol, 2-methylbutyl alcohol and 1-ethylpropyl alcohol.

The following amyl substituted barbituric acids have previously been prepared: *n*-amyl, *di-n*-amyl and *n*-amyl ethyl;[5] iso-amylmethyl, iso-amylethyl, iso-amyl-*n*-propyl, iso-amylisopropyl and di-iso-amyl;[6] iso-amylallyl;[3] ethyl-(1-ethylpropyl) and ethyl-(1-methylbutyl).[7]

In addition to the new isomeric amylbarbituric acid compounds which have now been prepared, two octyl derivatives were added to the list for comparison.

These compounds were tested, in comparison with barbital as a standard and with certain other known barbituric acid derivatives, by subcutaneous

[2] Tiffeneau, *Bull. soc. chim.*, [4] **33**, 183 (1923).

[3] Volwiler, THIS JOURNAL, **47**, 2236 (1925).

[4] Dox and Hjort, *J. Pharm. Exptl. Therap.*, **31**, 455 (1927).

[5] Dox and Jones, THIS JOURNAL, **50**, 2033 (1928).

[6] Carnot and Tiffeneau, *Compt. rend.*, **175**, 242 (1922); Shonle and Moment, THIS JOURNAL, **45**, 243 (1923).

[7] German Patent 293,163; Friedländer, **13**, 800 (1916–1921).

injections of solutions of the sodium salts according to the method previously described.[3,8]

Of this series of compounds, the most efficient are the ethyl-(1-methylbutyl) and the ethyl-(2-methylbutyl) derivatives. In sleep-producing efficiency in rats, the former compound seems to be the most active saturated alkylbarbituric acid that has been prepared. It is of interest that it is appreciably more efficient when tested on rats than the corresponding normal or iso compounds. These results also confirm the previously reported findings among the higher homologs of the barbituric acid series that increasing the size of the second alkyl group causes a decrease in hypnotic efficiency. Some comparative data, obtained by subcutaneous injections into rats, are given in the following table; an asterisk indicates that the data are taken from the literature.

	Hypnotic efficiency (Barbital = 1)		Hypnotic efficiency (Barbital = 1)
Ethyl-*n*-amyl	2.5	Di-*n*-amyl	0*
Ethyl-iso-amyl	3	Di-iso-amyl	1*
Ethyl-(2-methylbutyl)	3+	Allyl-*n*-amyl	1.25
Ethyl-(1-methylbutyl)	4.5	Allyl-iso-amyl	2.3+

Experimental Part

The intermediate malonic esters were prepared in the usual manner by the reaction of the alkyl bromide with malonic ester in the presence of sodium ethylate. The yields were from 70 to 85% of the theoretical. The disubstituted barbituric acids were prepared as usual by the reaction of the required disubstituted malonic ester with urea at 80–85°, in the presence of sodium ethylate. Most of the products were purified by recrystal-

TABLE I

PROPERTIES OF BARBITURIC ACID DERIVATIVES

Derivatives	Recryst. from	Properties of derivatives M. p., °C.	Nitrogen, % Calcd.	Found
n-Amylallyl	Water	97–100	11.76	11.78
Ethyl-(2-methylbutyl)	Pptd. from Na salt by CO_2	135–136	12.39	12.31
n-Butyl-(2-methylbutyl)	Dil. alcohol	146–148	11.03	10.91
n-Butyl-*n*-amyl	Alc., then pptd. from K salt by CO_2	118–120	11.02	10.80
Isopropyl-*n*-amyl	Water	100–102	11.67	11.57
Isobutyl-*n*-amyl	Alcohol	105–107	11.03	11.13
Isobutyl-iso-amyl	50% alcohol	146–147	11.03	10.90
Allyl-(2-methylbutyl)	Water	97–99	11.76	11.51
n-Butyl-(1-ethylpropyl)	Water	108–109	11.03	10.81
Ethyl-(1-methylbutyl)	Alcohol	129–130	12.39	12.36
n-Butyl-(1-methylbutyl)	Dil. alcohol	111–112	11.03	10.85
n-Butyl-(1-methylheptyl)	Dil. alc. or water	Indef.	9.45	9.35
Allyl-(1-methylheptyl)	Water or dil. alc.	148–150	10.0	10.4

[8] Nielsen, Higgins and Spruth, *J. Pharmacol. Exptl. Therap.*, **26**, 371 (1925).

TABLE I (*Concluded*)

PROPERTIES OF CORRESPONDING MALONIC ESTERS

Name	B. p., °C.	Mm.	Refr. index	Name	B. p., °C.	Mm.	Refr. index
n-Amyl	134–136	14	1.4240	*n*-Amyl-allyl	190–195	50	1.4372
2-Methylbutyl	150–152	45	1.4235	Ethyl-(2-methylbutyl)	160–165	37	1.4324
n-Butyl	235–240	760	1.4250	*n*-butyl-(2-methylbutyl)	165–170	22	1.4330
n-Butyl	235–240	760	1.4250	*n*-Butyl-*n*-amyl	185–193	55	1.4312
Isopropyl	211–215	760	1.4180	Isopropyl-*n*-amyl	186–190	50	1.4320
n-Amyl	134–136	14	1.4240	Isobutyl-*n*-amyl	184–192	47	1.4327
Iso-amyl	160–165	44	1.4230	Isobutyl-iso-amyl	170–176	35	1.4316
2-Methylbutyl	150–152	45	1.4235	Allyl-(2-methylbutyl)	154–167	26	1.4360
n-Butyl	235–240	760	1.4250	*n*-Butyl-(1-ethylpropyl)	155–170	40–50	1.4353
Ethyl	207–210	760	1.4200	Ethyl-(1-methylbutyl)	133–140	14	1.4329
n-Butyl	235–240	760	1.4250	*n*-Butyl-(1-methylbutyl)	145–150	20	1.4310
n-Butyl	235–240	760	1.4250	*n*-Butyl-(1-methylheptyl)	185–190	16	1.4410
1-Methylheptyl	195	57	1.4310	Allyl-(1-methylheptyl)	165	10	1.4370

TABLE II

SOLUTIONS OF THE SODIUM SALTS INJECTED SUBCUTANEOUSLY INTO WHITE RATS, EXPRESSED IN MILLIGRAMS OF THE BARBITURIC ACID PER KILOGRAM OF BODY WEIGHT

Barbituric acid derivative	Minimum effective dose (not awakened when outer ear passage is tickled with a straw)	Minimum lethal dose	Ratio, $\frac{\text{M. E. D.}}{\text{M. L. D.}}$
n-Amylallyl	160	250	0.64
Ethyl-(2-methylbutyl)	60	160	.375
n-Butyl-(2-methylbutyl)	Above 600	Above 600	
n-Butyl-*n*-amyl	Above 600	Above 600	
Isopropyl-*n*-amyl	150	290	.52
Isobutyl-*n*-amyl	410	Above 600	
Isobutyl-iso-amyl	400–450	Above 600	
Allyl-(2-methylbutyl)	80	170	.47
n-Butyl-(2-methylbutyl)	300–500	500	
Ethyl-(1-methylbutyl)	40 to 50	110	.41
Allyl-(1-methylheptyl)	Above 400	Above 400	
Diethyl	225	310	.72

lization from alcohol or water or a mixture of the two; in some cases purification was accomplished by dissolving the compounds in alkali and precipitating with acetic acid or carbon dioxide.

Summary

1. A series of isomeric amyl substituted barbituric acids has been prepared and the hypnotic activities pharmacologically compared.

2. The most effective of this series of compounds, injected subcutaneously in rats, are ethyl-(1-methylbutyl)-barbituric acid and ethyl-(2-methylbutyl)-barbituric acid.

NORTH CHICAGO, ILLINOIS