(Maule) were dried at 80–90°. A 1550-Gm. quantity of dried and ground plant was extracted in a Soxhlet extractor with petroleum ether (b.p. 65–75°) to exhaustion. This dark solution was concentrated to yield 50 Gm. of a dark green product. This product was refluxed for 1 hr. in a 5% sodium hydroxide ethanolic solution. The neutral product was found to be a polymethylenic alcohol of low melting point. The acidic fraction yielded, after several recrystallizations, 100 mg. of a compound, m.p. 273–275°; $[\alpha]_D^{20°}$ + 61° (pyridine c 0.45).

Alcoholic Extract—The defatted plant material was dried and the ethanol-soluble constituents were extracted. This dark solution was concentrated to yield 415 Gm. of a water-soluble product. This product was treated with 2.5 *N* ethanolic hydrochloric acid. The mixture was then refluxed for 5 hr. and poured into ice water. After 48 hr. the precipitate was collected on a filter and washed with water, yielding 215 Gm. of a light green mass. The crude ursolic acid was partially purified by continuous extraction, first with petroleum ether (b.p. 65–75°), then with a mixture of petroleum ether–benzene and, finally, with benzene. After recrystallizations of the product extracted with the mixture petroleum ether–benzene and benzene, 450 mg. of an acid, m.p. 267–279°, was obtained.

Ursolic Acid—Several recrystallizations of the previously obtained compound yielded ursolic acid, m.p. 281°; $[\alpha]_D^{20°}$ +61° (pyridine c 0.6), $\nu_{max.}^{KCl}$ 3350 and 1695 cm.$^{-1}$.

Ursolic Acid Acetate—The pure compound was obtained as needles after crystallization from methanol–chloroform, m.p. 281°.

Ursolic Acid Methyl Ester—This ester was prepared by diazomethane treatment of the acid in ethereal solution, crystallized from methanol–chloroform as colorless crystals, m.p. 170°; $\lambda_{max.}^{EtOH}$ 206 mμ ε 5000, $\nu_{max.}^{CHCl_3}$ 3410, 1754, and 1642 cm.$^{-1}$.

The melting point of this compound was undepressed upon admixture with an authentic specimen, m.p. 171°, and was found to be identical with the methyl ester of the acidic compound, m.p. 273–275°, previously isolated from the petroleum ether extract.

Ursolic Acid Methyl Ester Acetate—It was obtained as needles after crystallization from methanol–chloroform, m.p. 243–244°; $[\alpha]_D^{20°}$ +60° (chloroform c 0.48).

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Synthesis and Basic Pharmacology of *N*-Substituted and *N,N'*-Disubstituted Allyl Barbiturates

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***N*-Substituted and *N,N'*-disubstituted allyl derivatives of barbital, phenobarbital, hexobarbital, and diallylbarbital have been synthesized by the use of a strongly basic anion-exchange resin. The barbiturate is first absorbed on the resin and the resin then agitated mechanically with an ethanol solution of benzyl chloride. None of the allyl barbiturates approached phenobarbital in terms of pharmacological potency.**

In previous reports (1, 2) a method was described for the synthesis of benzyl ethers of a variety of phenols and of 5,5-disubstituted barbiturates by the use of a strongly basic anion-exchange resin. The method involved the reaction of the phenolate or the barbiturate form of the resin with benzyl chloride. The synthesis of the *N*-allyl and the *N,N'*-diallyl barbiturate derivatives seemed feasible, using this method, since the allyl and the benzyl halides are believed equally reactive chemically. This report presents an analogous method for the synthesis of *N*-allyl and *N,N'*-diallyl derivatives of four 5,5-disubstituted barbituric acids (phenobarbital, barbital, hexobarbital, and diallylbarbital) and the synthesis of 5,5-diallylbarbituric acid.

SYNTHESIS

The synthesis of these derivatives involved the reaction of the barbiturate form of a strongly basic anion-exchange resin with allyl bromide. The resin employed was a polystyrene polymer containing reactive quaternary ammonium groups. Proceeding at room temperature, a mixture of *N*-allyl and *N,N'*-diallyl derivatives was obtained from the reaction. Separation of the derivatives was effected by taking advantage of the solubility of the *N*-allyl derivative in dilute alkali. Table I presents the analytical data for allyl derivatives of barbituric acid, phenobarbital (5-ethyl-5-phenyl barbituric acid), barbital (5,5-diethyl barbituric acid), and hexobarbital (*N*-methyl-5-methyl-5-cyclohexenyl barbituric acid) prepared by the use of a strongly basic anion-exchange resin. The *N,N'*-diallyl derivative is the main product when an equivalency of the resin in the OH form is used with the barbiturate form and the quantity of the allyl bromide is doubled plus 10% excess.

Resin Preparation—Synthetic ion-exchange resin made from styrene-divinylbenzene copolymer[1] supplied commercially in the chloride form (20–50

Received December 13, 1966, from the College of Pharmacy, Butler University, Indianapolis, IN 46207
Accepted for publication April 20, 1967.
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[1] Dowex IX4, Dow Chemical Co., Midland, Mich.

TABLE I—ANALYSIS OF THE *N*-ALLYL AND *N,N'*-DIALLYL BARBITURATES

Compd.	Yield, %	M.p., °C.[b]	Empirical Formula	Anal.,[a] % Calcd.	Found
N-Allylbarbital	47	80–81[c]	$C_{11}H_{10}N_2O_3$	C, 58.93 H, 7.14 N, 12.50	59.13 7.40 12.46
N,N'-Diallylbarbital	30	120.5–121.5[d]	$C_{14}H_{20}N_2O_3$	C, 63.64 H, 7.57 N, 10.60	63.71 7.77 10.95
N-Allylphenobarbital	37	73.0–73.5[e]	$C_{15}H_{16}N_2O_3$	C, 66.14 H, 5.87 N, 10.29	65.92 5.96 10.24
N,N'-Diallylphenobarbital	35	40[f]	$C_{18}H_{20}N_2O_3$	C, 69.23 H, 6.41 N, 8.94	69.23 6.46 8.75
N-Allylhexobarbital	70	75–76[g]	$C_{15}H_{20}N_2O_3$	C, 65.19 H, 7.30 N, 10.14	65.43 7.33 9.94
5,5-Diallylbarbituric acid	45	169–170[h]	$C_{10}H_{12}N_2O_3$	C, 57.69 H, 5.77 N, 13.46	57.63 5.84 13.70
5,5,*N,N'*-Tetraallylbarbituric acid	25	148.5–149[i]	$C_{16}H_{20}N_2O_3$	C, 66.67 H, 6.94 N, 10.00	66.96 7.09 10.25

[a] Analyses were performed by Midwest Microlabs, Indianapolis, Ind., and Weiler and Strauss, Oxford, England. [b] Melting points were determined on a Fisher-Johns melting point apparatus. [c] Literature (4) 80°. [d] Literature (4) b.p. 156–157°. [e] Literature (4) 68–69°. [f] Literature (4) 40°. [g] Literature (4) 72°. [h] Literature (5) 169°. [i] Not reported in literature.

mesh), was converted to its hydroxyl form by the usual column technique with 5% aqueous sodium hydroxide (2, 3).

Absorption of the Barbiturate on the Resin—A general procedure was followed. The barbiturate as the sodium salt (0.05 mole) was dissolved in 300 ml. of distilled water and passed through a resin column 25 mm. in diameter. The resin was first rinsed with distilled water until the washings were neutral to phenolphthalein T.S., then with two 100-ml. portions of ethanol.

Synthesis of Allyl Barbiturates—A general procedure was followed for the synthesis of all allyl barbiturates. A description of the preparation of *N*-allyl and *N,N'*-diallylbarbital illustrates the procedure used.

N-Allylbarbital—A 4.1-ml. (0.041 mole) quantity of allyl bromide dissolved in 200 ml. of ethanol was added to the column containing the resin[1] (25 Gm.) upon which 7.0 Gm. (0.038 mole) of sodium barbital had been adsorbed. The mixture was then agitated for 48 hr. by rotating the column horizontally with an electric motor at 78 r.p.m. At the end of this period, the column was drained and the resin washed with three 75-ml. portions of ethanol. Evaporation of the eluate and washings left a yellow oily residue. The combined residue was dissolved in 30 ml. of ether and then extracted with 1 *N* sodium hydroxide solution. The alkaline aqueous portion, from which any *N,N'*-diallylbarbital was removed, was acidified with diluted hydrochloric acid and extracted with several portions of ether. The combined ether extractives were washed free of acid and evaporated to dryness. A crystalline residue was obtained which, when recrystallized from 50% methanol in water, melted at 80–81°. [Lit. (4) m.p. 80°.] The yield was 3.75 Gm. (47%).

Anal.—Calcd. for $C_{11}H_{20}N_2O_3$: C, 58.93; H, 7.14; N, 12.50. Found: C, 59.13; H, 7.40; N, 12.46.

N,N'-Diallylbarbital—A 6.6-ml. (0.066 mole) quantity of allyl bromide dissolved in 200 ml. of ethanol was added to the column containing the resin[1] (25 Gm.) upon which 6.18 Gm. (0.03 mole) of sodium barbital had been adsorbed. The mixture was agitated as described previously. At the end of this period, the column was drained and the resin washed with ethanol. The ethanolic solution was evaporated down to a yellow oily residue. The residue was washed with 1 *N* sodium hydroxide solution and extracted with several portions of ether. Evaporation of the ether extractives, first washed free of alkali, yielded *N,N'*-diallylbarbital which, when crystallized from 50% methanol in water, melted at 121°. [Lit. (4) b.p. 156–157°.] The yield was 2.65 Gm. (30%).

Anal.—Calcd. for $C_{14}H_{20}N_2O_3$: C, 63.64; H, 7.57; N, 10.60. Found: C, 63.71; H, 7.77; N, 10.95.

PHARMACOLOGY

Preparation—Each of the barbiturates was suspended, with the aid of a motorized Ten Broeck tissue homogenizer, in 25 ml. of distilled water containing 1% w/v of methylcellulose (1500 cps.). The resulting suspensions were diluted to 50 ml. with water yielding stock preparations containing 0.5% methylcellulose and 10^{-3} moles of barbiturate per ml. of suspension. Further dilutions were made, when necessary, with a 0.5% methylcellulose vehicle.

Animals—Male albino mice, 18–28 Gm., were employed as test subjects. They were selected from stock colonies of 200–300 animals and isolated 1–2 hr. prior to drug administration. Tests were conducted in rooms having an air temperature of 24–26°.

Standard—Phenobarbital was adopted as the reference standard against which the allyl barbiturates were compared.

Protocol—Mice were weighed, injected intra-

TABLE II—INFLUENCE OF ALLYL BARBITURATES ON THE RIGHTING REFLEX OF MALE MICE

Drug	Nominal Mol. Wt.	Dose mole/Kg.	Dose mg./Kg.	Incidence of R.R. Loss	Mean Onset Time, min.	Mean Duration, min.
Phenobarbital	232	3×10^{-4}	70	1/8	39[a]	107[a]
		5×10^{-4}	116	8/8	25	134
		7×10^{-4}	162	8/8	17	532
N-Allylphenobarbital	272	3×10^{-4}	91	0/8	...	...
		5×10^{-4}	136	2/8	13	15
		7×10^{-4}	194	8/8	11	40
N,N'-Diallylphenobarbital	312	5×10^{-4}	156	0/8	...	...
		7×10^{-4}	218	0/8	...	...
		1×10^{-3}	312	0/8	...	...
		2×10^{-3}	624	0/8	...	...
N-Allylbarbital	224	5×10^{-4}	112	0/8	...	...
		7×10^{-4}	157	1/8	20[a]	36[a]
		1×10^{-3}	224	8/8	4	334
N,N'-Diallylbarbital	264	5×10^{-4}	132	0/8	...	...
		7×10^{-4}	184	0/8	...	...
		1×10^{-3}	264	5/16	6	18
N-Allylhexobarbital	276	5×10	138	0/8	...	...
		7×10	193	0/8	...	...
		1×10	276	0/8	...	...
		2×10	552	0/8	...	...
Tetraallylbarbituric acid	288	5×10^{-4}	144	0/8	...	...
		7×10^{-4}	201	0/8	...	...
		1×10^{-3}	288	0/8	...	...
		2×10^{-3}	576	0/8	...	...

[a] One animal.

peritoneally with the appropriate doses of barbiturate (maximum volume injected was 0.6 ml.), and placed in individual 4-L. glass observation chambers. The animals were observed continuously during the first 4-hr. postinjection and periodically during the next 20-hr. period for the appearance of behavioral symptoms characteristic of barbiturate medication, *e.g.*, prodromal excitation, sedation, loss of righting reflex.

Results—A summary of the results is presented in Table II. In terms of both subtle and gross evidence of CNS depression, none of the allyl barbiturates approached phenobarbital in potency. *N*-Allylphenobarbital, *N*-allylbarbital, and *N,N'*-diallylbarbital exhibited mild hypnotic action at doses below those necessary to influence the righting reflex. The first instances of righting reflex loss occurred at 3×10^{-4} mole/Kg. (phenobarbital), 5×10^{-4} mole/Kg. (*N*-allylphenobarbital), 7×10^{-4} mole/Kg. (*N*-allylbarbital), and 10^{-3} mole/Kg. (*N,N'*-diallylbarbital). The most active depressant among the allyl barbiturates was *N*-allylphenobarbital. *N,N'*-Diallylphenobarbital evoked only the mildest degree of sedation and doses up to 2×10^{-3} mole/Kg. failed to influence the righting reflex. *N*-Allylhexobarbital and tetraallylbarbituric acid were devoid of all obvious CNS actions at doses up to 2×10^{-3} mole/Kg.

The appearance of mild prodromal excitability characterized the initial response to several of the compounds. Phenobarbital induced the characteristic locomotor excitability in mice at doses of 5×10^{-4} mole/Kg. and higher. Similar but less intense effects were observed when 7×10^{-4} mole/Kg. of *N*-allylphenobarbital was administered. *N*-Allylbarbital induced a severe clonus of short duration in animals receiving doses above 7×10^{-4} mole/Kg. The remaining compounds evoked no evidence of CNS stimulation.

The ranking of depressant potencies of the allylbarbiturates is in good agreement with the ranking of acute LD_{50}'s reported by Kaku *et al.* (4). Gylys and Proctor (6) examined the anticonvulsant properties of *N*-allylbarbital and *N*-allylphenobarbital. They reported that *N*-allyl substitution on barbital increased anticonvulsant activity but decreased duration of action while *N*-allyl substitution on phenobarbital decreased anticonvulsant activity both in terms of intensity and duration. Doses of the two drugs at which activity was observed were in the range of 50–100 mg., concentrations too low to alter the righting reflex.

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