TABLE II.—PLASMA LEVELS OF C^{14}-LABELED 1815, I.S. IN RABBITS

Injection	Time, min.	C^{14} 1815, I.S., mcg./ml. Control Mean ± S.E.[a]	C^{14} 1815, I.S., mcg./ml. Pretreated with SKF 525-A Mean ± S.E.[a]
SKF 525-A, 10 mg./Kg. i.v.	−10	...	...
	0	...	...
C^{14} 1815, I.S. 0.25 mg./Kg. i.v.			
	1	3.22 ± 0.73	2.71 ± 0.70
	5	1.48 ± 0.29	1.52 ± 0.66
	10	0.94 ± 0.34	1.26 ± 0.45
	20	...	...
C^{14} 1815, I.S. 0.25 mg./Kg. i.v.			
	21	3.44 ± 1.57	4.40 ± 1.41
	25	2.04 ± 0.99	3.01 ± 1.58
	30	1.78 ± 1.01	2.76 ± 1.80

[a] Five rabbits used in each case.

to, and detachment from, receptors is important for stimulation would also be compatible with the present findings. This would mean that the SKF 525-A is increasing the rate at which the neuromuscular blocker-receptor combination is being made and broken without having influence on the total amount of drug being present.

Evidence that SKF 525-A itself has an effect upon neuromuscular transmission and receptor excitability have been found by a number of authors (3, 9, 10). This makes it quite difficult to separate clearly the action(s) of SKF 525-A involved in the observed potentiation of neuromuscular blocking agents. Further attempts will be necessary to clarify this problem.

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Synthesis of N-Substituted and N,N′-Disubstituted Benzyl Derivatives of 5,5-Disubstituted Barbiturates

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N-Substituted and N,N′-disubstituted benzyl derivatives of barbital, phenobarbital, and amobarbital 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. The reaction proceeds at room temperature. The yields in all cases ranged from 50 to 80 per cent.

IN A PREVIOUS REPORT (1) a method was described for the synthesis of benzyl ethers of a variety of phenols by the use of a strongly basic anion-exchange resin. The method involved the reaction of the phenolate form of the resin with benzyl chloride. This report presents an analogous method for the synthesis of N-benzyl and N,N′-dibenzyl derivatives of three 5,5-disubstituted barbituric acids (phenobarbital, barbital, and amobarbital). The synthesis of these derivatives involves the reaction of the barbiturate form of a strongly basic anion-exchange resin with benzyl chloride. The resin employed is based on polystyrene and contains quaternary ammonium groups. The reaction proceeds at room temperature. A mixture of N-benzyl and N,N′-dibenzyl derivatives is obtained from the reaction. Separation of the derivatives is based upon the solubility of the N-benzyl derivative in dilute alkali. Table I summarizes the benzyl derivatives of phenobarbital (5-ethyl-5-phenyl barbituric acid), barbital (5,5-diethyl barbituric acid), and amobarbital (5-ethyl-5-isoamyl barbituric acid) prepared by the use of a strongly basic anion-exchange resin. The yields are based upon the amount of the barbiturate converted to the N-benzyl and N,N′-dibenzyl derivatives. The N,N′-dibenzyl 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 benzyl chloride is doubled.

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EXPERIMENTAL

Resin Preparation.—Dowex 1X4[1] supplied commercially in the chloride form (20–50 mesh) was converted to its hydroxyl form by the usual column

[1] Manufactured by Dow Chemicel Co., Midland, Mich., and purchased from J. T. Baker Co., Phillipsburg, N. J.

TABLE I.—BENZYL DERIVATIVES OF 5,5-DISUBSTITUTED BARBITURIC ACIDS BY THE USE OF A STRONGLY BASIC ANION-EXCHANGE RESIN

Barbiturate	Yield, % 50 meq. Dowex 1×4 (barbiturate form) 0.075 mole benzyl chloride	Yield, % 50 meq. Dowex 1×4 (barbiturate form) 50 meq. Dowex 1×4 (OH form) 0.15 mole benzyl chloride	M.p., °C.[a]	Anal.[b] Calcd.	Found
Phenobarbital, N-benzyl	47.6	19.6	112.5[c]	C 70.81	70.65
				H 5.59	6.05
				N 8.70	8.90
Phenobarbital, N,N′-dibenzyl	31.0	48.5	90[d]	C 75.73	75.65
				H 5.83	6.10
				N 6.80	6.89
Barbital, N-benzyl	32.3	6.57	127[e]	C 65.70	65.26
				H 6.57	6.59
				N 10.22	10.35
Barbital, N,N′-dibenzyl	37.9	74.7	124[f]	C 72.53	72.00
				H 6.97	7.00
				N 7.69	7.64
Amobarbital, N-benzyl	19.62	9.5	90[g]	C 68.35	67.88
				H 7.60	7.76
				N 8.86	8.79
Amobarbital, N,N′-dibenzyl	33.5	53.3	53[h]	C 73.84	74.32
				H 7.38	7.56
				N 6.90	7.04

[a] All melting points on calibrated Fisher-Johns apparatus. [b] Carried out by Weiler and Strauss, Oxford, England. [c] Literature (3) m. p. 113°. [d] Not reported in literature. [e] Literature (3, 4) m.p. 127°. [f] Not reported in literature. [g] Literature (5) m. p. 89–90°. [h] Literature (6) oil.

technique with 5% aqueous sodium hydroxide (four to five times the volume of resin). The resin was rinsed with distilled water until the washings were neutral and then with absolute methanol. The residual methanol was removed by passing a current of carbon dioxide-free air through the column of resin. The quantity of resin employed for each run of benzyl derivatives was based upon the absorption capacity of the resin determined by the method of Kunin and Myers (2).

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. distilled water and passed through the resin in a column 25 mm. in diameter. The resin column 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 Benzyl Barbiturates.—A general procedure was followed for the synthesis of the benzyl barbiturates. The preparation of N-benzyl and N,N′-dibenzyl phenobarbital illustrates the procedure used.

An 18.9-Gm. (0.15 mole) quantity of benzyl chloride dissolved in 300 ml. ethanol was added to the column containing the Dowex 1X4 resin (43 Gm.), upon which 11.6 Gm. (0.05 mole) of phenobarbital U.S.P. had been absorbed. The mixture was then agitated for 48 hours by rotating the column horizontally with an electric motor at 75 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 yellowish syrupy residue containing a mixture of N-benzyl and N,N′-dibenzyl phenobarbital.

N,N′-Dibenzyl Phenobarbital.—Separation of N,N′-dibenzyl phenobarbital was accomplished by treating the yellowish syrupy residue with 1 *N* sodium hydroxide solution and extracting the resulting alkaline-aqueous mixture with several portions of ether. Evaporation of the ether extractives, first washed free of alkali, yielded N,N′-dibenzyl phenobarbital which when crystallized from 95% ethanol melted at 90°. The yield was 6.41 Gm. (31%).

Anal.—Calcd. for $C_{26}H_{24}N_2O_3$: C, 75.73; H, 5.88; N, 6.80. Found: C, 75.65; H, 6.10; N, 6.89.

N-Benzyl Phenobarbital.—The alkaline-aqueous portion from which the N,N′-dibenzyl phenobarbital 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 70% ethanol melted at 112.5°; literature (3) m.p. 113°. The yield was 7.66 Gm. (47.6%).

Anal.—Calcd. for $C_{19}H_{18}N_2O_3$: C, 70.81; H, 5.59; N, 8.70. Found: C, 70.65; H, 6.05; N, 8.90.

SUMMARY

A method is presented for the synthesis of N-benzyl and N,N′-dibenzyl derivatives of three 5,5-disubstituted barbituric acids by the use of a strongly basic anion-exchange resin. The barbiturate form of the resin is treated with an ethanol solution of benzyl chloride. The reaction proceeds at room temperature.

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