ethyl phenylmalonate[21] and compound 33 from diethyl β-phenoxyethylmalonate.[22]

The 5-alkoxyalkyl-5-phenylbarbituric acids (compounds 31, 34, 35 and 37, Table II) were obtained, in the manner illustrated below, by the use of magnesium methylate[23] as a condensation agent; all other barbituric acids were prepared by the usual procedure with the aid of sodium ethylate in the presence of toluene.

**5-(β-Methoxyethyl)-5-phenylbarbituric Acid.**—Magnesium methoxide was obtained when 0.94 g. (0.040 mole) of magnesium ribbon, which had been cleaned with steel wool and cut into small pieces, was refluxed with 50 cc. of absolute methyl alcohol until all of the metal had reacted. After the addition of 10 g. (0.039 mole) of diethyl β-methoxyethylphenylmalonate and 3.3 g. (0.055 mole) of urea, the mixture was refluxed for twenty-four hours, the alcohol removed and the residue acidified with 18% hydrochloric acid. A small amount of unchanged malonic ester was removed by extraction with low boiling petroleum ether. The barbituric acid weighed 7.5 g. (73%).

(21) "Organic Syntheses," Vol. 16, p. 34.

(22) Bentley, Haworth and Perkin (*J. Chem. Soc.*, **69**, 167 (1896)) did not report the boiling point; we found the latter to be 215–218° (30 mm.).

(23) This agent was first employed in the barbituric acid synthesis by Lund (*Kgl. Dan. Vid. Selsk. Math.-fys. Medd.*, **13**, 13 (1935)); *Ber.*, **69**, 1621 (1936).


## Summary

The preparation and hypnotic activity of a number of 5,5-disubstituted barbituric acids which contain an arylalkyl, cycloalkylalkyl, alkoxyalkyl or aryloxyalkyl group have been described.


ANN ARBOR, MICHIGAN RECEIVED AUGUST 4, 1941

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF DELAWARE]

# Barbiturates Containing Large Radicals

BY GLENN S. SKINNER AND A. P. STUART[1]

It has been reported that α-alkyl-α-carbethoxy-γ-butyric lactones[2] condense very easily with urea to give excellent yields of 5-alkyl-5-β-hydroxyethylbarbiturates. This observation encouraged us to try the condensation of such lactones containing large radicals where solvent effects might be expected to interfere.

These experiments were successful, but some experimental items deserve especial mention. In fractionally distilling the higher lactones under diminished pressure it is quite necessary to release the vacuum very slowly when changing receivers. Otherwise a violent explosion may occur as the rarefied vapor is heated above its spontaneous ignition temperature. After removal of the bulk of the unchanged alkylmalonic ester, it is highly desirable to distill the remainder from a flask the neck of which is immersed in the bath up to the side tube. During the condensation with urea the object to be attained is the solution of the maximum amount of the lactone while some of the urea is still undissolved.

## Experimental Part

Lauryl,[3] cetyl[4] and octadecylmalonic esters[5] were synthesized by standard procedures using the corresponding alcohols and malonic ester as starting materials. It may be noted that the yield of the alkyl malonic ester may be increased from about 75% to about 85% by the simple expedient of gradually adding the alkyl bromide dissolved in a second mole of malonic ester: lauryl ester, b. p. 170–172° (2 mm.); cetyl ester, b. p. 195–200° (1 mm.); octadecyl ester, b. p. 200–205° (1 mm.).

**Lactones.**—The lactones were prepared by the procedure previously described.[2] The desirability of using two equivalents of the alkylmalonic ester was checked. If only one mole of the lauryl ester is used, the yield of the lactone drops from 81 to 55%.

LACTONES $C_2H_5O_2C-\underset{R}{\overset{|}{C}}(-CH_2-CH_2-O)-C(=O)$

| R— | B. p., °C. | Mm. | M. p., °C. | Yield, % | Found, % C | Found, % H | Calculated, % C | Calculated, % H |
|---|---|---|---|---|---|---|---|---|
| *n*-$C_{12}H_{25}$-[a] | 192–194 | | 43.5 | 81 | 70.5 | 10.6 | 70.1 | 10.5 |
| *n*-$C_{16}H_{33}$- | 225–230 | 0.3 | 49 | 84 | 72.3 | 11.1 | 72.3 | 11.1 |
| *n*-$C_{18}H_{37}$- | 233–238 | 0.4 | 55–56 | 73 | 72.4 | 11.3 | 73.1 | 11.3 |

[a] $d^{25}_4$ 0.9680 (supercooled liquid); $d^{50}_4$ 0.9505; $d^{75}_4$ 0.9325.

**5-Alkyl-5-β-hydroxyethyl Barbiturates.**—Since unsatisfactory results are likely to be obtained without close attention to experimental details, the procedure for the preparation of 5-octadecyl-5-(β-hydroxyethyl)-barbituric acid is recorded. In a typical run, 3.45 g. (0.15 mole) of sodium is dissolved in 40 cc. of absolute alcohol, and the solution is cooled to 10–15° with stirring as part of the sodium ethoxide crystallizes. The stirring is continued at a rate to avoid splashing while 20.5 g. (0.05 mole) of α-octadecyl-α-carbethoxy-γ-butyric lactone and 6.05 g. (0.10 mole) of urea are added at once in the order named at the point of the stirrer. The water surrounding the reaction flask is heated at such a rate that after an hour the

(1) Present address: Sun Oil Company, Norwood, Pa.

(2) Skinner, THIS JOURNAL, **59**, 322 (1937).

(3) Rothstein, *Bull. soc. chim.*, [5] **2**, 80–90 (1935).

(4) Phillips and Mumford, *J. Chem. Soc.*, 1736 (1931).

(5) Bleyberg and Ulrich, *Ber.*, **64**, 2509 (1931).

temperature has risen to 35° and most of the solids have passed into solution. After two hours the temperature should be 45°, and some of the product will have begun to crystallize. The temperature should be 70° after twelve hours, and a large amount of the product then will have crystallized.

The alcohol is removed under diminished pressure, and the residue is dissolved in a liter of water. The solution is cooled and acidified with hydrochloric acid. The dry crude product weighs 21 g., contains the hydroxy acid as an impurity, and melts at 95–110°. After crystallization from 110 cc. of ligroin and 30 cc. of chloroform, it melts at 135–150°. It requires a second crystallization from 150 cc. of a 2:1 alcohol–water mixture and a third from 50 cc. of chloroform and 10 cc. of ligroin to raise the melting point to the constant value of 150°. The yield of pure product is 17.5 g.

It is not practical to remove the hydroxy acid from the cetyl and octadecyl derivatives by extraction with sodium bicarbonate solution on account of the troublesome emulsion. This is a suitable procedure for the lauryl derivative. However, one crystallization of the dry crude lauryl derivative from hot absolute alcohol gives a good product. In using the same slow heating process but double the quantity of alcohol the yield of the lauryl derivative drops from 82 to 68%.

**5-Alkyl-5-(β-bromoethyl) Barbiturates.**—In using the method of preparation previously reported, a difficulty arises in that the hydroxyethyl barbiturates do not dissolve in the fuming hydrobromic acid as in the case of the lower homologs. The following modification applied to the octadecyl derivative gave a yield of 70%.

5-Octadecyl-5-(β-hydroxyl)-barbituric acid (25 g.), chloroform (50 cc.), and 70% hydrobromic acid (100 cc.) are heated in a soda water bottle for four hours at 50–60°. The crude product weighs 27 g. and melts at 98–102°. After crystallizing once from dilute alcohol and twice from a 1:2 chloroform–ligroin mixture, there is obtained a pure product weighing 20 g. and melting at 104.5°.

5-ALKYL-5-(β-HYDROXYETHYL) BARBITURATES

| Alkyl | M. p., °C. | Yield, % | Found N, % | Calcd. N, % |
|---|---|---|---|---|
| $n$-$C_{12}H_{25}$- | 145 | 82 | 8.29 | 8.23 |
| $n$-$C_{16}H_{33}$- | 147 | 83 | 7.06 | 7.07 |
| $n$-$C_{18}H_{37}$- | 150 | 81 | 6.62 | 6.60 |

5-ALKYL-5-(β-BROMOETHYL) BARBITURATES

| Alkyl | M. p., °C | Yield, % | Bromine, % Calcd. | Found |
|---|---|---|---|---|
| $n$-$C_{12}H_{22}$- | 101.5 | | 19.72 | 19.66 |
| $n$-$C_{16}H_{33}$- | 102.5 | 65 | 17.01 | 17.08 |
| $n$-$C_{18}H_{37}$- | 104.5 | 70 | 16.40 | 16.33 |

## Summary

α-Alkyl-α-carbethoxy-γ-butyric lactones have been employed in the synthesis of barbiturates containing large radicals at position five.

NEWARK, DELAWARE RECEIVED JULY 22, 1941

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[CONTRIBUTION FROM ALLERGEN INVESTIGATIONS, BUREAU OF AGRICULTURAL CHEMISTRY AND ENGINEERING, U. S. DEPARTMENT OF AGRICULTURE]

# The Chemistry of Allergens. V. The Amino Acid Content of Active Protein and Polysaccharidic Protein Fractions from Cottonseed[1]

BY JOSEPH R. SPIES

This paper presents results of the determination of the amino acid content of allergenic fractions obtained in a previously described electrophoretic fractionation[1] of CS-1A.[2] CS-1A proved to be a mixture consisting of specifically active protein and compounds of this protein containing polysaccharidic carbohydrate in varying proportions. Fractions CS-51R, and CS-52R, which migrated toward the cathode, contained less than 1% carbohydrate while the anodic fraction CS-56H contained 37% carbohydrate. Quantitatively determined among the hydrolytic products of these fractions were cystine, histidine, arginine, lysine, glutamic acid, tyrosine, humin, and ammonia. Results are summarized in Table I.

## Discussion

The protein component of CS-1A appears to be analogous to the "natural proteoses" from vegetable sources which Wells and Osborne studied.[3] These authors, however, did not determine the amino acid content of their proteoses.

On the basis of available analyses Mitchell and

(1) (a) Paper IV of this series, Spies, Bernton and Stevens, THIS JOURNAL, **63**, 2163 (1941). The cottonseed used in this and previous investigations in this Laboratory was choice quality, dehulled, American grown, seed of the Upland Group. This material should therefore be designated *Gossypium hirsutum* rather than *Gossypium herbaceum* as reported in Paper I of this series. S. C. Harland, "The Genetics of Cotton," Jonathan Cape, London (1939). (b) Not copyrighted.

(2) Spies, Coulson, Bernton and Stevens, THIS JOURNAL, **62**, 1420 (1940).

(3) Wells and Osborne, *J. Infectious Diseases*, **17**, 259 (1915). Their proteoses were apparently distinct from other reserve proteins of seeds, possessed strong anaphylactogenic activity and were stable to heating to 100°. These authors stated "They resemble highly soluble native proteins in their anaphylactic capacity and are probably quite as complex in their chemical constitution." The cottonseed allergen is, however, more diffusible than the proteoses of Wells and Osborne, indicating lower molecular weight. A paper describing antigenic properties of cottonseed allergenic fractions has appeared elsewhere; Coulson, Spies and Stevens, *J. Immunol.*, **41**, 375 (1941).