Research Article

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The synthesis of new barbiturate esters derivatives as intravenous anesthetics: a new dimension of anesthesia route part-III

Abstract

Conventional 1-methyl-2-oxybarbiturates and 1-methyl-2-thiobarbiturates are employed as anesthetics and tend to accumulate in the body due to their slow rate of metabolism. As a result, the use of these compounds is restricted to either being an induction agent for anesthesia, subsequently maintained by volatile anesthetics, or for short surgical procedures only. To overcome these limitations of barbiturates as general anesthetics, and to avoid the use of volatile agents, structural modifications of barbiturates molecules as intravenous anesthetics were attempted. It was conceived that, by incorporating metabolically labile ester functions in one or both of the side chain of the barbiturates ring system, this could be achieved. Since this procedure could diminish the likelihood of barbiturates to be accumulated in the body, it would make it possible to get safer barbiturate intravenous anesthetics. This classification arose from the observation that while the biological properties of some drugs are extremely sensitive to minor changes in the stereo-chemical feature, electron distribution, and substituent, there are many other drugs which exhibit similar patterns of biological behavior, despite a wide diversity in their chemical configurations. This has appeared to be the case with the barbiturate esters as discussed.

Keywords: barbiturates, intravenous anesthetics, metabolically labile ester

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Introduction

The synthesis and preliminary biological investigations of eighteen (18) barbiturates containing ester function, in one of the side chains have been reported in this communication. A few related barbiturates, needed for the synthesis of esters, have also been reported. The currently accepted explanation of the short action of barbiturate anesthetics is the distribution of drugs into the tissues and fats within the body compartments and to some degree of metabolism. It is, however, known that barbiturate anesthetics are not rapidly metabolized in the body but are instead accumulated in the tissues and fats making elimination a slow process thus causing hangover among patients. The investigator, therefore, assumed that it could be possible to provide anesthetics barbiturate through molecular modifications which would undergo rapid metabolism and thereby offer critical clinical advantages. It was thought that there was a need for a potent and fast-acting agent which, because of the rapid metabolic breakdown and elimination from the body, allows the restoration of mental faculties within a short period after surgery and without a persistent hangover or a headache. The first barbiturate used as an intravenous anesthetic was hexobarbitone which was quickly replaced by short-acting thiopentone. However, its use remained only to simple surgical procedures, lasting for a very brief period, because of its very short duration of action. Since Thiopentone tends to accumulate in the body, its use was limited to that of an induction agent only, and substantial precautions had to be taken by the anesthetists given its low therapeutic index. Considering these complex properties of barbiturates molecules, it was assumed that molecular modifications could alter the properties of barbiturates by improving their lipid solubility. This could be achieved either by introducing alkyl or aryl groups in side chain or ring nitrogen atoms or by replacing one of the ring oxygen with sulfur or selenium. Mauttner[1] reported that by increasing the side length to up to eight carbon atoms, both potency and lipid solubility rise. Beyond eight carbon atoms, results either produce convulsion or inactive compounds. The probable explanation is that the lipid solubility of the drug molecule reached such a level that it accumulated in body fats and could not reach its receptors.

The presence of ester function in many drugs like cholinergic, anti-cholinergic and local anesthetics are responsible for their susceptibility to the action of plasma esterase, and these drugs are rapidly metabolized and quickly eliminated from the body. Further, the introduction of ester functions in the decamethylene chain of the neuromuscular blocking agent decamethonium has been exploited to overcome the prolonged action of the compound. The resulting drug Suxamethonium is widely used in surgery. Given the above discussion, a pragmatic plan was undertaken, and 6 and 31 barbiturate ester derivatives were synthesized, analyzed and their biological investigation was conducted on mice, rats and in some cases rabbits and reported in two instalments.[2,3] Following is a list of eighteen new barbiturate esters derivatives, along with their biological results (Table 1–5) & (Figure 1–5).

Table 1

Compound No	R	π	Es	σ*	Dose mg/kg	% Anesthesia	Duration in mins	% depth
80	$-CH_2C_6H_5$	2.27	-0.38	0.22	100	-	-	20
81	$-CH(CH_3)_2$	1.30	-0.47	-0.19	100	-	-	10
					200	-	-	
82	$-(CH_2)_2CH_3$	1.5	-0.36	-0.12	100	-	-	60(100)
					200	100	9	

Table 2

Compound no	R	π	Es	σ*	Dose mg/kg	% Anesthesia	Duration in mins	% depth
83	$-(CH_2)_6CH_3$	4.5			100[c]	-	-	50
84	$-(CH_2)_{10}CH_3$	5.5			100[c]	-	-	70

Table 3

Compound no	R	π	Es	σ*	Dose mg/kg	% Anesthesia	Duration in mins	% depth
85	Cyclo-C_6H_{11}	2.51	-0.79	-0.15	30	-	-	100
					100	-	-	100
86	$-CH(C_6H_5)C_2H_5$	3.07	-1.5	0	100	-	-	
					200	100	21	40(100)
87	$-CH(C_6H_5)_2$	3.84	-1.76	0.41	100	-	-	
					200	100	14.5	20
88	$-(CH_2)_6CH_3$	3.5	(-0.40)	(-1.75)	100	-	-	
					200	-	-	100
89	$-(CH_2)_4CH_3$	2.5	-0.47	(-0.15)	100	-	-	50
90	$C_9H_8O_2$			0.41	50	-	-	10
					100	-	-	100
91	-nepthyl				100	-	-	
					200	-	-	100

Table 4

Compound no	R	π	Es	σ*	Dose mg/kg	% Anesthesia	Duration in mins	% depth
92	0	0.5	0	0	100	-	-	20(40)
					200	-	-	
93	$-C_2H_3$	1	-0.07	-0.1	200	-	-	10
94	$-(CH_2)_2CH_3$	1.5	-0.36	-0.12	100	-	-	
					200	-	-	50
95	$-CH_2C_6H_5$	2.27	-0.38	0.22	100[c]	-	-	50(40)

Table 5

Compound no	R	π	Es	σ*	Dose mg/kg	% Anesthesia	Duration in mins	% depth
96	$-CH_2C_6H_5$	2.27	-0.38	0.22	100	-	-	
					200	10	2.6	
97	$-(CH_2)_2CH_3$	1.5	-0.38	-0.12	100	-	-	
					200[c]	-	-	
98	$-CH(CH_3)_2$	1.30	-0.47	-0.19	100	-	-	
					200	-	-	

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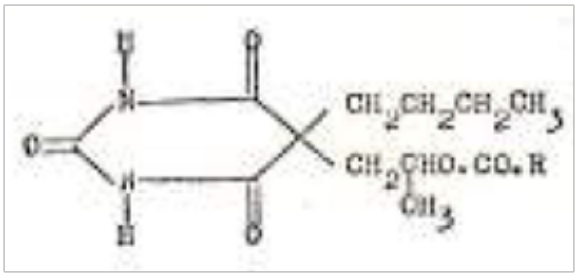

Figure 1

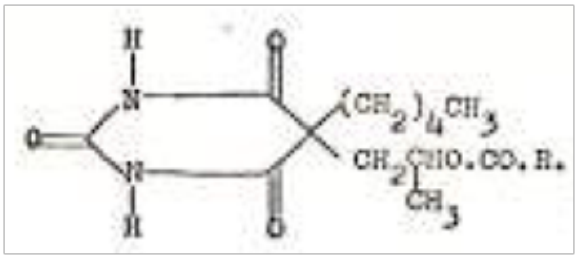

Figure 2

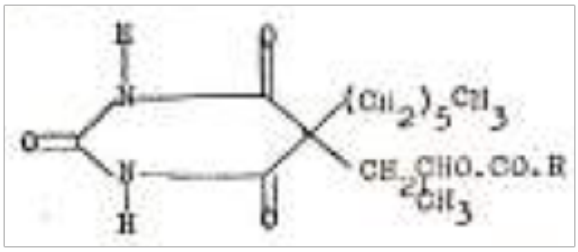

Figure 3

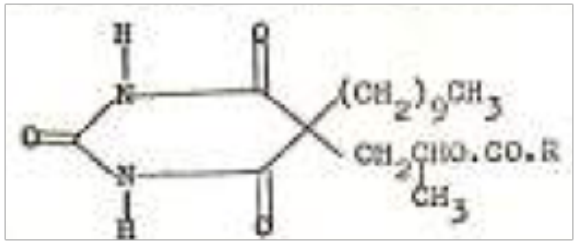

Figure 4

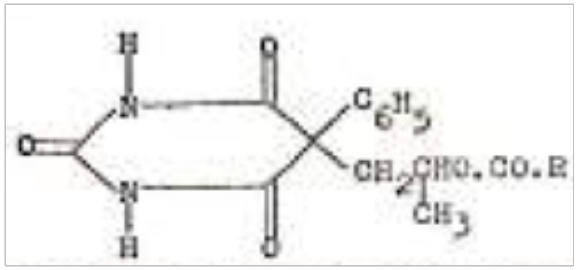

Figure 5

Experimental design

Melting points

Melting points were recorded either in Kofler Heizbank type 184321 or Reichert's microscopic melting point apparatus.

Thin layer chromatography: Silica gel plates were used except where specifically stated otherwise. Both extemporaneously prepared plates (MN-Duren, MN-kieselgel G-HR) and MN-Duren, polygram SilG /UV_{254} plates were found to be satisfactory.

Development solvent: A mixture of Chloroform and Acetone in the ratio of 1:1.

Spray reagent: Plates were sprayed with a saturated aqueous solution silver acetate, dried and then sprayed with 10% diphenyl carbazone aqueous solution to which a required quantity of ethanol was added to assist dissolution of solute. The barbiturate esters appeared as lilac spots on the chromatogram.

Preparation of sodium salts of barbiturate esters: The barbiturate ester was dissolved in an equivalent normal sodium hydroxide solution. The addition of a certain amount of ethanol was often necessary to ensure complete dissolution of the ester. Once the ester had completely dissolved, the solvent was removed under reduced pressure. The sodium salt thus obtained was taken up in a minimum volume of distilled water and extracted with ether to remove any unchanged free ester. Water was removed under vacuum, and a small quantity of ethanol was added to the residue in order to zoetrope off any traces of water. The dry powder of sodium salt of barbiturate ester was then stored in a tightly sealed container and kept in a desiccator.

Esters derived from barbiturate alcohols

Synthetic procedure: A literature search revealed that 5-alkyl-5-allyl barbiturate could be converted to 5-alkyl-5-(2-hydroxypropyl)-barbiturate. Thus, [5-{(2R)-pentan-2-yl(5-prop-2enyl-1,3-diazinane-2,4,6-trione)}] (quinalbarbitone) and [5-5-diprop-2-enyl-1,3-diazinane-2,4,6-trione] (allobarbitone) were converted into 5-{(1-methylbutyl)-(2-hydroxypropyl)} barbituric acid (A) and 5-{allyl-5-(2-hydroxypropyl)} barbituric acid(B) respectively. These hydroxyl barbiturates were transformed to esters by introducing different alkyl and aryl groups, their structures were confirmed by chemical analysis, and biological screening was carried out.

Synthesis of 5-(1-methylbutyl)-5-(2-hydroxypropyl) barbituric acid alcohol (A): 25g of quinalbarbitone was taken in RB flask; 25 ml conc. Sulfuric acid was added into it at RT (25^{0}C) and stirred continuously for 30 minutes. The deep red colored solution was put into a conical flask containing 200ml iced water. After keeping this for about 30-45 minutes, a crystalline solid appeared which was filtered, washed with iced cooled water, dried in air for 2-3 hours and finally dried at 60-70^{0}C for 2 hours and purified to get compound (A) (Figure 6).

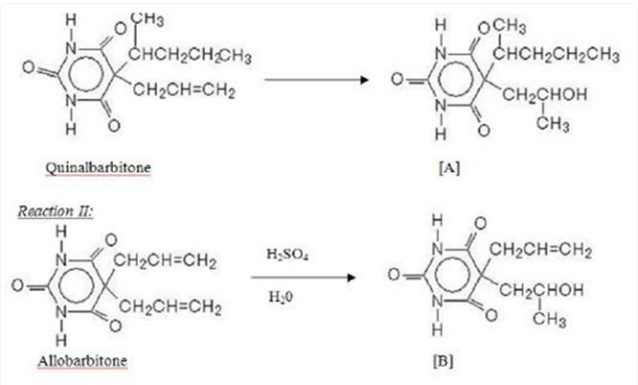

Figure 6 Synthesis of 5-(1-methylbutyl)-5-(2-hydroxypropyl) barbituric acid alcohol (A)

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Purification of compound (A): The solid product thus obtained was dissolved in boiled water, and activated charcoal (5-7%) was added to the hot solution, stirred for 10 minutes and the charcoal filtered off. On cooling the filtrate at RT, fine crystals of compound (A) appeared. This was washed with hot water and dried in the oven at 80-85^{0}C to get moisture free white crystalline compound (20g;74.5%), mp.191-93^{0}C (lit.204^{0}C).

Analysed: Found C, 56.60; H, 7.90; N, 10.85 and O, 24.65. $C_{12}H_{22}N_2O_4$ requires**:** C, 56.00; H, 7.90, N, 10.90 and O, 25.2%. Rf. value 0.50.

Compound number: refers to Experimental protocol numbers.

Synthesis Compound number (80): 5-Butyl-5-(2-hydroxypropyl) barbituric acid phenyl acetate

The barbiturate Alcohol (42A) 2g and phenyl acetate 1.23g were refluxed in the presence of Conc. Sulfuric acid as for (52).[4] The 2% ethanol in ether eluate from basic alumina column chromatography was evaporated and crystallized from ether-petroleum ether (40-60^{0}C) to give fine crystals barbiturate ester(80); (1.51g, 50%) mp. 134-35^{0}C.

Synthesis of compound number (81): **5-Butyl-5-(2-hydroxypropyl) barbituric acid isobutyrate:** The procedure applied was the same as the one used for compound 80 with the exception of using isobutyric acid to give the ester 81, (1.3g; 50%), mp. 137-39^{0}C.

Synthesis of compound number (82): 5-Butyl 5-(2-hydroxypropyl) barbituric acid butyrate: The barbiturate Alcohol 2g butyric acid 0.72g were refluxed with a few drops Conc. Sulfuric acid. After column chromatography using basic alumina and working out as comp. 81 yielded an oil which on crystallization gave needles of comp. 82 (1.4g; 54%) mp. 133-35^{0}C**.** Found: C, 57.95; H, 7.65; N, 9.2%. $C_{15}H_{24}N_2O_5$ requires C,57.70; H,7.7; N, 9.0%; R_F O.60.

Synthesis of compound number (83): 5-pentyl-5-(2-hydroxypropyl) barbituric acid decanoate: The barbiturate alcohol 42d (2g) and decanoic acid (2g) were refluxed in the presence of concentrated sulphuric acid, as described for 52. The 2% ethanol in ether fraction from basic alumina on crystallization from ether-petroleum ether (40-60^{0}C) gave needles of 5-pentyl-5-(2-hydroxypropyl) barbituric acid decanoate (1.4g, 46%), m.p. 115-116^{0}C (Found: C, 64.2; H, 9.2; N, 7.0. $C_{22}H_{38}N_2O_5$ requires C, 64.4; H, 9.25 N, 6.8%).

Synthesis of compound number (84): 5-pentyl-5-(2-hydroxypropyl) barbituric acid laurate: The barbiturate alcohol 42d (2g) and lauric acid (2g) were refluxed with a few drops of concentrated sulphuric acid, as for 52. The 2% ethanol in ether eluate from basic alumina was evaporated and crystallized from ether-petroleum ether (40-60^{0}C) to give 5-pentyl-5-(2-hydroxypropyl) barbituric acid laurate (1.4g, 43%) as fine needles, m.p. 108-110^{0}C (found: C, 65.7; H, 9.6; N, 6.7. $C_{24}H_{42}N_2O_5$ requires C, 65.75; H, 9.6 and N, 6.4%).

5-Hexyl-5-allylbarbituric acid: Diethyl allyhexylmalonate, (100g) and urea (25.3g) were refluxed in freshly prepared sodium ethoxide solution (Na, 8.5g) as for ethyl allylbarbituric acid. The resulting oily product chromatographed on basic alumina, and the ether eluate on concentration gave needles of the barbituric acid (54g, 61%), m.p.148-150^{0}C.

5-Hexyl-5-(2-hydroxypropyl)barbituric acid (42e): 5-Hexyl-5-allylbarbituric acid (30g) was treated with concentrated sulphuric acid (30g) as described for 42a. The resulting product was washed with water and dried in an oven at 100^{0}C. This was then recrystallized from aqueous methanol to give the barbituric acid (25g, 78%) m.p. 178-180^{0}C, R_F 0.34.

Synthesis of compound number (85): **5-Hexyl-5-(2-hydroxypropyl) barbituric acid cyclohexanoate:** The barbiturate alcohol 42e (2g) and cyclohexane carboxylic acid (2g) and cyclohexane carboxylic acid (2g) were refluxed with a few drops of concentrated sulphuric acid, as described for 52. The 2% ethanol in ether eluate from basic alumina gave an oil which, after evaporation of the solvent was crystallized form ether-petroleum ether (40-60^{0}C) to give needles of 5-Hexyl-5-(2-hydroxypropyl)barbituric acid cyclohexonate (1.7g, 60%), m.p. 153-154 (Found: C, 63.4; H, 8.5; N, 7.4. $C_{20}H_{32}N_2O_5$ requires C, 63.1 ; H, 8.4 and N, 7.4%) R_F 0.66.

Synthesis of compound number (86): **5-Hexyl-5-(2-hydroxypropyl) barbituric acid 2-phenyl-butyrate:** The barbiturate alcohol 42e (2g) and 2-phenylbutyric acid (2g) were refluxed in the presence of concentrated sulphuric acid as for 52. The 2% ethanol in ether eluate from basic alumina gave the barbiturate ester (1.62g, 52.5%) as an oil, R_F 0.66 (single spot).

Synthesis of compound number (87): 5-Hexyl-5-(2-hydroxypropyl) barbituric acid diphenyl-acetate: The barbiturate alcohol 42e (2g) diphenylacetic acid (2g) and a few drops of concentrated sulphuric acid were refluxed, as described for 52. The 2% ethanol in other fraction from basic alumina gave the barbiturate ester (1.6g, 46.5%) as an oil, R_F 0.66 (single spot).

Synthesis of compound number (88): 5-Hexyl-5-(2-hydroxypropyl) barbituric acid octanoate: The barbiturate alcohol 42e (2g) was dissolved in octanoic acid (2ml) and the solution was refluxed in the presence of concentrated sulphuric acid, as described for 48. The 2% ethanol in ether eluate from basic alumina on crystallization from ether-petroleum ether (40-60^{0}C) gave needles of 5-Hexyl-5-(2-hydroxypropyl)barbituric acid octanoate (1.7g, 58%), m.p. 123-124 (Found: C, 63.6; H, 9.2; N, 7.1. $C_{21}H_{36}N_2O_5$ requires C, 63.6; H, 9.1 and N, 7.0%), R_F 0.69.

Synthesis of compound number (89): 5-Hexyl-5-(2-hydroxypropyl) barbituric acid hexanoate: The barbiturate alcohol 42e (2g) was refluxed in excess of hexanoic anhydride (4ml), as described for 49. The 2% ethanol in ether eluate from basic alumina on crystallization from ether-petroleum ether (40-60^{0}C) gave colorless plates of 5-Hexyl-5-(2-hydroxypropyl)barbituric acid hexanoate (1.44, 53%), mp. 108-110 (Found : C, 62.2; H, 8.6; N, 7.5. $C_{19}H_{32}N_2O_5$ requires C, 61.95; H, 8.7 and n, 7.6%), R_F 0.69.

Synthesis of compound number (90): **5-Hexyl-5-(2-hydroxypropyl) barbituric acid cinnamate:** The barbiturate alcohol 42e (2g), cinnamic acid (2g) and a few drops of concentrated sulphuric acid were refluxed as described 52. The resulting product was chromatographed on basic alumina and the 2% ethanol in ether eluate on crystallization from ether-petroleum ether (40-50^{0}C) gave colourless plates of 5-Hexyl-5-(2-hydroxypropyl)barbituric acid cinnamate (1.43g, 48%), m.p. 155-157^{0}C (Found: C, 65.65; H, 7.2; N, 6.9. $C_{22}H_{28}N_2O_5$ requires C, 66.0; H, 7.0 and N, 7.0%), R_F 0.67.

5-Synthesis of compound number (91): Hexyl-5-(2-hydroxypropyl) barbituric acid α-naphthylacetate: The barbituric alcohol α-naphthyl-acetic acid (2g) and a few drops of concentrated sulphuric acid were refluxed, as for the 52. The 2% ethanol in ether fraction from basic alumina on crystallization from ether-petroleum ether (40-60^{0}C) yielded colorless plates of 5-Hexyl-5-(2-hydroxypropyl)barbituric

acid α-naphthyl acetate (1.3g, 40%), mp. 165-167^{0}C (Found: C, 68.5; H, 6.8 and N,6.4%).

5-Decyl-5-allylbarbituric acid: Diethyl allyldecylmalonate (170g) and urea (41g) were refluxed in freshly prepared sodium ethoxide solution (Na, 11.5g) as for ethyl allylbarbituric acid. The resulting thick oil was crystallized from ether to give needles of the barbituric acid (85g, 50%) m.p. 98-100^{0}C.

5-Decyl-5-(2-hydroxypropyl) barbituric acid (42): 5-Decyl-5-allylbarbituric acid (25g) was treated with concentrated sulphuric acid (25g) as for 42A. The resulting product was washed with water and dried in an oven at 100^{0}C. This was recrystallized from aqueous methanol to give the barbiturate acid (16g, 60%), m.p. 150-152^{0}C.

Synthesis of compound number (92): 5-Decyl-5-(2-hydroxypropyl) barbituric acid acetate: The barbiturate alcohol 42A (2.5g) was refluxed in acetic anhydride (6ml) as described for 49. The 2% ethanol in ether eluate from basic alumina on crystallization from ether-petroleum ether (40-60^{0}C) gave 5-Decyl-5-(2-hydroxypropyl) barbituric acid acetate (1.7g, 57%) mp. 115-117^{0}C (Found: C, 62.0; H, 8.4; N, 7.9. $C_{19}H_{32}N_2O_5$ requires C, 62.0; H, 8.7 and N, 7.6%), R_F 0.59.

Synthesis of compound number (93): 5-Decyl-5-(2-hydroxypropyl) barbituric acid propionate: The barbiturate alcohol 42A (2.5g) and propionic anhydride (6ml) were refluxed for 6h, as for 49. The 2% ethanol in ether eluate from basic alumina was evaporated and then crystallized from ether-petroleum-ether (40-60^{0}C) to give 5-Decyl-5-(2-hydroxypropyl) barbituric acid propionate (1.8g, 58%), m.p. 109-111^{0}C (Found: C, 62.6; H, 8.9; N, 7.25. $C_{20}H_{34}N_2O_5$ requires C, 62.6; H, 8.9 and N, 7.3%), R_F 0.60.

Synthesis of compound number (94): 5-Decyl-5-(2-hydroxypropyl) barbituric acid butyrate: The barbiturate alcohol (42A) 2.5g was refluxed in butyric anhydride 6ml for about 5-6h. The column chromatographic fraction in 2% ethanol was crystallized from ether-petrolium ether (40-60^{0}C), afforded compound 94, 1.69g; 53%, mp. 103-104^{0}C. Found: C, 63.50; H, 8.80; N,7.3%. $C_{21}H_{36}N_2O_5$ requires; C, 63.60; H, 9.00 and N, 7.00%. R_F 0.63.

Synthesis of compound number (95): 5-Decyl-5-(2-hydroxypropyl) barbituric acid phenyl acetate: The barbiturate alcohol 2.5g, phenyl acetic acid 3g and a few drops Conc. Sulfuric acid was refluxed for 6h and on working out as previously afforded compound 95, 1.56g, 43% mp. 93-95^{0}C. Found: C, 67.60; H, 8.20 and N, 6.5%. $C_{25}H_{36}N_2O_5$ requires: C, 67.70; H, 8,10 and N,6.30%. R_F 0.59.

Synthesis of 5-phenyl-5-allyl barituric acid: Diethyl allyl phenylmalonate 130g and saturated ethanolic solution of urea 34.8g refluxed in freshly prepared sodium ethoxide solution (Na, 13g). The resulting oily product was crystallized from diethyl ether to give needles of 5-phenyl-5-allyl barbituric acid, (47g, 41%), mp.153-55^{0}C.

Synthesis of 5-phenyl-5-(2-hydroxypropyl) barbituric acid: 5-Phenyl-5-allyl barbituric 14.70g was treated with Conc. Sulfuric as for 42A and the resulting product was washed with water and in on oven at 100^{0}C. The compound was re-crystallized from methanol to give fine needles 5-phenyl-5-(2-hydroxypropyl) barbituric acid, 12.70g; 80%, mp.255-56^{0}C. Found: C, 60.00; H,5.40 and N,11.00. $C_{13}H_{14}N_2O_4$ requires: C, 59.50; H, 5.30 and N, 10.70%.

Synthesis of 5-phenyl-5-(2-hydroxypropyl) barbituric acid phenyl acetate(96): The barbiturate alcohol (42A) 2g, phenyl acetic acid 1.40g and a few drops Conc. Sulfuric was refluxed for 6h and worked as other esters which gave crystalline compound (96) (1.36 g; 47.0%0, mp. 170-71^{0}C. Found: C, 66.15, H, 5.40 and N, 7.70%. $C_{21}H_{20}N_2O_5$ requires C, 66.30; H,5.25 and 7.40%.

Synthesis of 5-phenyl-5-(2-hydroxypropyl) barbituric acid butyrate(97): The barbiturate alcohol (42A) 2.0g, butyric acid 0.73g along with a few drops of Conc. Sulfuric acid were refluxed for 6h and the reacted product was worked out as for other esters which afforded the crystalline product (1.45g; 57%), mp 187-88^{0}C. Found: C,61.80; H,6.00 and N,8.60%. $C_{17}H_{20}N_2O_5$ requires C, 61.40; H,6.00 and 8.40%. R_F 0.59.

Synthesis of 5-phenyl-5-(2-hydroxypropyl) barbituric acid iso-butyrate(98): This synthesis is similar to that of compound 87 except that of using iso butyric acid instead of butyric acid. Analytical and physical data: yield 1.40g; 56.0%, mp 194-96^{0}C. Found: C, 61.40; H,6.00 and N,8.50%. $C_{17}H_{20}N_2O_5$ requires: C, 61.40; H, 6.00 and N, 8.40%

Results and discussion

It is evident from the results that even where the pie values of the 5-alkyl side chain varies only marginally from that of the 1-methylbutyl group, the compounds tested are either inactive or with low potency. The actual pie values used in tables V-IX are as follows:

Tables	Substituent	Pie values
I	$-(CH_2))_3CH_3$	2
2	$-(CH_2)_4CH_3$	2.5
3	$-(CH_2)_5CH_3$	3
4	$-(CH_2)_9CH_3$	5

The absence of correlation between potency and 5-alkyl substituent was not expected. It remains a matter of speculation whether or not some degree of structural specificity was involved in the action of barbiturate esters described here. However, the superiority of 1-methylbutyl substituent clearly emerged from the reported results and this group became the mainstay of future strategy, as will be seen from further discussion. While the present work was in progress, a communication Smissman[4] reported the synthesis of a series of barbiturate esters as potential long-acting central nervous system depressants. Four of their compounds were identical with the compounds described here. Their research presents a directly opposing view as to the expected effect of incorporating an ester function into the barbiturate side chain with regards to the duration of action. Smissman[4] published biological data did not indicate the duration action of his compounds, but four of these compounds were prepared in the course of this work. The potency and duration of action are given in table X which shows that they are shorter acting pento barbitone which has duration of action of 26.25 minutes at the 100% anesthetic dose of 40mg/kg i.p in mice. Table 1–5 list[1,2] many barbiturate esters which exhibit a brief duration of action. However, none of these compounds were deemed to be of potential clinical importance given the somewhat low potency when compared with drugs such as methohexitone on mice used in the screening of the esters in communication. All barbiturate esters reported here were biologically tested on male mice (CFLP) usually in groups of ten (18-22g). Drugs were administered intravenously as sodium salts in physiological saline unless otherwise stated. Letters m, w and c in tables stand for 5% mulgofen, carbon dioxide free distilled water and convulsion respectively. Percentage death figure in tables refers to acute toxicity, whilst delay toxicity (over 24 hours) has been shown in

brackets. Certain compounds were administered to rats in groups of ten (CHFB-Wister, 50-70g) and Rabbits, Dutch Albino (1-2kg).

Conclusion

In order to obtain a comprehensive understanding of barbiturate esters as Intravenous Anesthetics, an extensive investigation is necessary on Barbiturate derivatives and their related esters of similar or diverse structural compounds.

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Conflicts of interest

The author declares that there is no conflicts of interest.

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