Cyclization Reactions Leading to β-Hydroxyketo Esters

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Abstract □ The purpose of the research was to synthesize β-diketo esters and to evaluate them for anticonvulsant activity. The reaction of methyl vinyl ketone with dimethyl malonate in the presence of potassium carbonate gave an uncyclized product that underwent a Claisen condensation to yield methyl 2-hydroxy-4-oxocyclohex-2-en-1-oate (**5a**). Similarly, other cyclized β-hydroxyketo esters were prepared, and their spectrometric data confirmed that the enol tautomers were preferred to the β-diketo tautomers. The synthetic work clarified the reaction pathway for the Michael addition of malonate esters to enones. Of the intermediates and products tested for anticonvulsant activity, dimethyl 2,2-bis-(3-oxobutyl)malonate (**9a**) was found to possess anticonvulsant property. However, it is emphasized that the β-hydroxyketo esters could be useful intermediates in the synthesis of enaminone anticonvulsants.

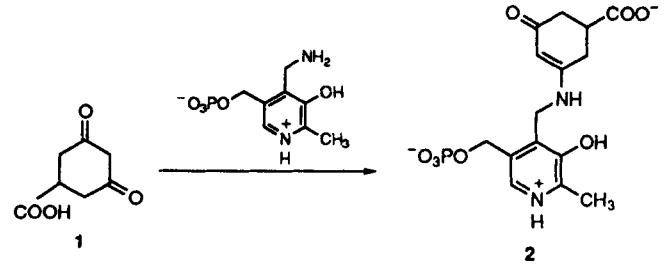
By virtue of the presence of two carbonyl groups and their tendency towards enolization, β-diketones offer the possibility of keto–enol tautomerism, dual reactivity, formation of intramolecular hydrogen bonds, and the synthesis of useful intermediates.[1] In the design of potential anticonvulsant agents, 3,5-dioxocyclohexanecarboxylic acid (**1**) was identified as a Class IV γ-aminobutyric (GABA) aminotransferase (GABA-T) inactivator.[2,3] GABA-T converts GABA into succinic acid via succinic semialdehyde, but when GABA-T is inactivated, the brain level of GABA becomes elevated and anticonvulsant activity is enhanced.[2] The GABA-T inactivation occurs when **1** forms a Schiff base **2** with pyridoxamine phosphate (PMP), the cofactor on which GABA-T is dependent (Scheme 1).

It appeared feasible to synthesize β-diketo esters the chemical structures of which were similar to **1**. Therefore, several β-diketo esters were prepared via a cyclization reaction. The spectral characteristics of the intermediates and the β-diketo esters were determined and evaluated for anticonvulsant activity.

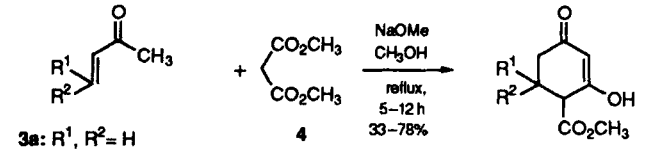
Results and Discussion

Generally, cyclization reactions between vinyl ketones (**3a–3d**) and dimethyl malonate (**4**) result in the formation of β-diketo esters (**5a–5d**; Scheme 2). However, the Michael addition of methyl vinyl ketone (**3a**) to diethyl malonate (**6**) in the presence of sodium ethoxide has been reported[4] to yield the uncyclized **7b**, which reacted further to give a mixture of **8**, **9b**, and **10** (Scheme 3). In the explanation for the formation of the bicyclic acid **10**, the presence of the intermediate **9b** was assumed. Of interest was the analogous intermediate **9a** that was isolated in low yield in this work. To prevent uncyclized **7a** and **7b** from reacting further to produce a mixture of products, it was desirable to isolate and purify them. Thus, the intermediate that underwent Claisen condensation to the β-hydroxyketo ester **5a** was the keto diester **7a** that was initially isolated and purified after a potassium carbonate catalyzed reaction.

Compared with the cyclocondensation of dimethyl malonate (**4**) with 3-penten-2-one (**3b**; Scheme 2), it was equally convenient to obtain the β-hydroxyketo ester **5b** from ethyl crotonate (**11**)



Scheme 1—Inactivation of GABA-T by 3,5-dioxocyclohexanecarboxylic acid.



3a: R^1, R^2 = H
3b: R^1 = H, R^2 = CH_3
3c: R^1 = H, R^2 = C_6H_5
3d: R^1, R^2 = CH_3

5a: R^1, R^2 = H
5b: R^1 = H, R^2 = CH_3
5c: R^1 = H, R^2 = C_6H_5
5d: R^1, R^2 = CH_3

Scheme 2—Synthesis of β-hydroxyketo esters from vinyl ketones and dimethyl malonate.

and methyl acetoacetate (**12**), as shown in Scheme 4.[5] Benzylidene acetone (**3c**) was reacted with dimethyl malonate (**4**) in the presence of potassium carbonate to yield the uncyclized adduct **13**, the cyclized adduct **5c**, and the decarboxylated product **14**. It was possible to isolate the three products from the reaction (Scheme 5) after an acid–base extraction. The ^1H NMR spectra of the β-hydroxyketo esters **5a–5d** showed chemical shifts of δ 5.00–5.60 for the vinyl protons, whereas the IR spectra displayed an enol OH at ~3460, an ester C=O at ~1730, and C=C absorption at ~1600 cm^{-1}. Compounds **5**, **15**, and **16** existed in tautomeric equilibrium, in which **5** was the β-diketo tautomer, as in Scheme 6, but the spectral data indicated that the β-diketo esters **5** existed predominantly in the enol forms **15** and **16**. The stability of the enol forms **15** and **16** is increased by intramolecular and intermolecular hydrogen bonding, respectively.

Of the intermediates and the β-hydroxyketo esters tested for anticonvulsant activity, only one compound (**9a**) was found to possess anticonvulsant property in the mouse.[6] Compound **9a** protected the mouse against electrically induced seizures at 30 min after pretreatment with an intraperitoneal injection of a 300-mg/kg dose (Table 1).

After noting the report that enaminones of β-hydroxyketones were very stable and could act as potential prodrugs,[7] the use of β-hydroxyketo esters **5a–5d** in the design of enaminone anticonvulsants was investigated and a structure–activity relationship was established.[5]

Conclusions—The synthesis of the β-hydroxyketo esters clarified the reaction pathway for the Michael addition of malonate esters to vinyl ketones. On their own, the β-hydroxyketo esters displayed no convulsant, anticonvulsant, or motor

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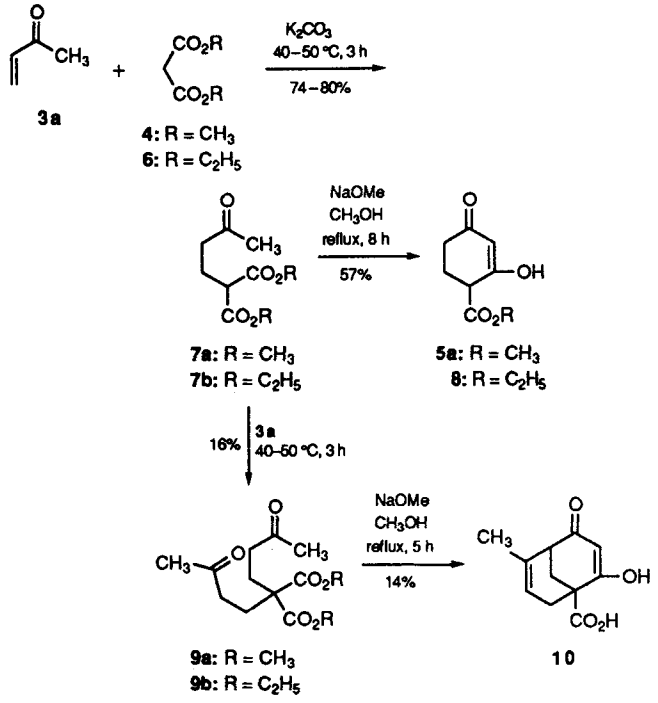
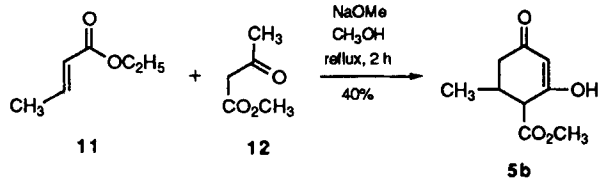
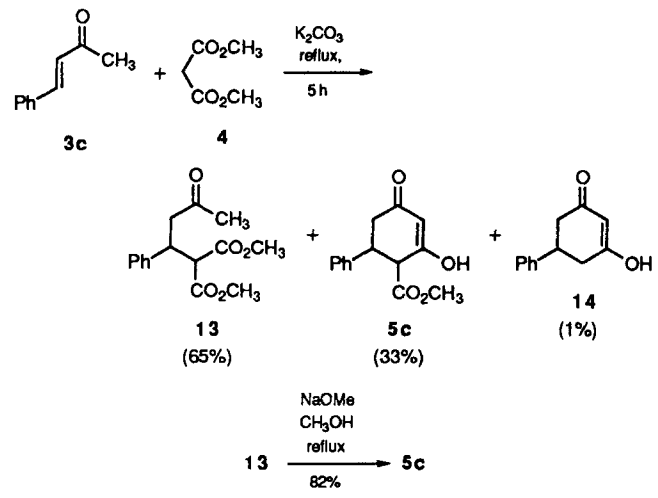


Scheme 3—Reaction pathways indicating the desired products (**5a** and **8**) that were formed when the intermediates (**7a** and **7b**) were isolated, as compared with the bicyclic compound (**10**) obtained when the intermediates (**7a** and **7b**) remained in the reaction mixture.

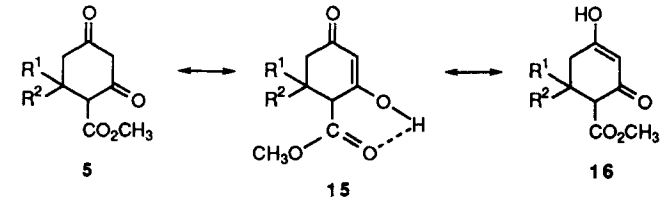


Scheme 4—Synthesis of a β-hydroxyketo ester (**5b**) from ethyl crotonate (**11**) and methyl acetoacetate (**12**).



Scheme 5—Uncyclized (**13**) and cyclized products (**5c** and **14**) obtained from the reaction between *trans*-benzylidene acetone (**3c**) and dimethyl malonate (**4**).

impairment when evaluated for central effects in the Antiepileptic Drug Development Program.[6] Only one intermediate, **9a**, possessed anticonvulsant activity against electrically induced seizures in mice. However, the β-hydroxyketo esters were found



Scheme 6—Tautomerism between β-diketo esters (**5**) and β-hydroxyketo esters (**15** and **16**).

Table 1—Anticonvulsant Screening Project (ASP) Phase I Test Results

		Activity						
		MES[a]		scMet[b]		Tox[c]		
Compound	Dose, mg/kg	30 min	4 h	30 min	4 h	30 min	4 h	ASP Classification[d]
5a	30	0/1	0/1	0/1	0/1	0/4	0/2	3
	100	0/3	0/3	0/1	0/1	0/8	0/4	
	300	0/1	0/1	0/1	0/1	0/4	0/2	
5b	30	0/1	0/1	0/1	0/1	0/4	0/2	3
	100	0/3	0/3	0/1	0/1	0/8	0/4	
	300	0/1	0/1	0/1	0/1	0/4	0/2	
5c	30	0/1	0/1	0/1	0/1	0/4	0/2	3
	100	0/3	0/3	0/1	0/1	0/8	0/4	
	300	0/1	0/1	0/1	0/1	0/4	0/2	
5d	30	0/1	0/1	0/1	0/1	0/4	0/2	3
	100	0/3	0/3	0/1	0/1	0/8	0/4	
	300	0/1	0/1	0/1	0/1	0/4	0/2	
7a	30	0/1	0/1	0/1	0/1	0/4	0/2	3
	100	0/3	0/3	0/1	0/1	0/8	0/4	
	300	0/1	0/1	0/1	0/1	0/4	0/2	
9a	30	0/1	0/1	0/1	0/1	0/4	0/2	2
	100	0/3	0/3	0/1	0/1	0/8	0/4	
	300	1/1	0/1	0/1	0/1	0/4	0/2	
13	30	0/1	0/1	0/1	0/1	0/4	0/2	3
	100	0/3	0/3	0/1	0/1	0/8	0/4	
	300	0/1	0/1	0/1	0/1	0/4	0/2	

[a] Maximal electroshock test (number of animals protected/number of animals tested). [b] Subcutaneous pentylenetetrazol test. [c] Rotorod toxicity. [d] 1, anticonvulsant activity at 100 mg/kg or less; 2, anticonvulsant activity at 300 mg/kg; 3, inactive at 300 mg/kg.

to be useful intermediates in the preparation of enaminone anticonvulsants.[5]

Experimental Section

General—Reagents and starting materials were obtained from Aldrich Chemical Company and were used without further purification. Melting points (mps) were measured in open capillary tubes and are uncorrected. The UV spectra were determined with a Pye-Unicam SP 800 spectrophotometer, and IR spectra of solids (KBr) and liquids (film) were determined with a Perkin-Elmer 297IR spectrophotometer. The ^1H NMR spectra were determined on a General Electric QE 300-MHz spectrometer in deuterated solvents using tetramethylsilane as an internal standard [coupling constants (*J*) are rounded to the nearest Hz]. Coupling patterns are described as follows: s, singlet; bs, broad singlet; d, doublet; t, triplet; m, multiplet; and 1H, 2H, 3H, etc. (the number of hydrogens was integrated within a given coupling pattern). Microanalyses were performed by Elemental Microanalysis Limited, Beaworthy, Devon, U.K. or by Schwarzkopf Microanalytical Laboratory, Woodside, NY. The anticonvulsant evaluation was carried out by the Antiepileptic Drug Development Program of the National Institutes of Health, Bethesda, MD.

Methyl 2-Hydroxy-4-oxocyclohex-2-en-1-oate (5a)—To a freshly prepared solution of sodium (5.7 g, 0.25 g-atom) in methanol (65 mL)

was added dimethyl 2-(3-oxobutyl)malonate (**7a**, 50.5 g, 0.25 mol). The reaction mixture was stirred on an ice bath for 1 h and then refluxed for 8 h. After partitioning between saturated sodium chloride solution (250 mL) and diethyl ether (250 mL), the aqueous layer was acidified with sulfuric acid (150 mL, 1 M) and extracted with dichloromethane (2 × 250 mL). The combined extracts were dried over anhydrous magnesium sulfate, evaporated, and crystallized from diethyl ether to yield methyl 2-hydroxy-4-oxocyclohex-2-en-1-oate (**5a**, 24 g, 57%): mp 82–84 °C (from toluene) (Lit.[8] mp 81–82 °C); ^{1}H NMR ($CDCl_3$): δ 2.30–3.60 (m, 5H, 2 × CH_2 + CH), 3.74 (s, 3H, OCH_3), 5.54 (s, 1H, =CH), 8.47 (bs, 1H, OH).

Methyl 2-Hydroxy-6-methyl-4-oxocyclohex-2-en-1-oate (5b)—The procedures (Schemes 2 and 4) previously described[5] afforded methyl 2-hydroxy-6-methyl-4-oxocyclohex-2-en-1-oate (**5b**) in a yield of 4.9 g (44%): mp 122–123 °C (from ethyl acetate); UV: λ_{max} (ε): (ethanol) 254 (17 000) nm; IR (chloroform): ν 3150 (br, OH), 3020 (CH), 1730 (C=O), 1650, 1610 cm^{-1}; ^{1}H NMR (CD_3COCD_3): δ 1.09 (d, 3H, J = 6 Hz, CH_3), 2.50 (m, 2H, CH_2), 3.12 (m, 2H, 2 × CH), 3.76 (s, 3H, OCH_3), 5.33 (s, 1H, =CH), 10.10 (bs, 1H, OH).

Dimethyl 2-(3-Oxo-1-phenylbutyl)malonate (13), Methyl 2-hydroxy-4-oxo-6-phenylcyclohex-2-en-1-oate (5c), and 3-Hydroxy-5-phenylcyclohex-2-enone (14)—*Method 1*—To a mixture of 4 (13.2 g, 0.1 mol) and anhydrous potassium carbonate (5 g, 36 mmol) was added trans-4-phenyl-3-buten-2-one (14.6 g, 0.1 mol) with stirring. The reaction mixture was refluxed for 5 h, cooled, and neutralized with hydrochloric acid (50 mL, 1 M). Sodium hydroxide solution (100 mL, 2.5 M) was added, and the reaction mixture was extracted with dichloromethane (2 × 100 mL), dried over anhydrous magnesium sulfate, and evaporated to give dimethyl 2-(3-oxo-1-phenylbutyl)malonate (**13**, 18 g, 65%): mp 63–64 °C (from diethyl ether); IR (chloroform): ν 2950 (CH), 1740 (C=O), 1720 (C=O), 1360, 760 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.00 (s, 3H, CH_3), 2.88 (s, 1H, CH), 2.98 (s, 1H, CH) , 3.45 (s, 3H, OCH_3), 3.66 (s, 3H, OCH_3), 3.75 (s, 2H, CH_2), 7.25 (m, 5H, C_6H_5).

Anal.—Calcd ($C_5H_{18}O_5$) C, H.

The aqueous layer was acidified with hydrochloric acid (50 mL, 2.5 M), extracted with dichloromethane (2 × 100 mL), dried over anhydrous magnesium sulfate, and evaporated to give methyl 2-hydroxy-4-oxo-6-phenylcyclohex-2-en-1-oate (**5c**, 8 g, 33%): mp 159–161 °C (from toluene); UV: λ_{max} (ε): (ethanol) 257 (23 200) nm; IR (chloroform): ν 3150 (br, OH), 1720 (C=O), 1650, 1600 (C=C), 1525 cm^{-1}; ^{1}H NMR (CD_3COCD_3): δ 2.70 (m, 2H, CH_2), 3.42 (s, 3H, OCH_3), 3.70 (m, 2H, 2 × CH), 5.45 (s, 1H, =CH), 7.35 (m, 5H, C_6H_5), 10.28 (bs, 1H, OH).

Anal.—Calcd ($C_{14}H_{14}O_4$) C, H.

The aqueous layer was neutralized to pH 7 with sodium hydroxide (10 mL, 2.5 M) and left to stand for 5 d whereupon white crystals were collected and recrystallized from toluene to give 3-hydroxy-5-phenylcyclohex-2-enone (**14**, 0.2 g, 1%): mp 188–190 °C (from toluene) (Lit.[9] mp 183–185 °C); IR (KBr): 1720, 1710, 1660, 1600, 1580, 1525 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.45 (s, 2H, CH_2), 2.56 (s, 2H, CH_2), 3.20 (m, 1H, CH), 5.40 (s, 1H, =CH), 8.30 (m, 5H, C_6H_5).

Method 2—To a freshly prepared solution of sodium (6 g, 0.26 g-atom) in methanol (100 mL) was added **13** (72 g, 0.26 mol) with constant stirring on an ice bath. The reaction mixture was stirred at room temperature for 30 min and refluxed for 2 h with vigorous stirring. After cooling, saturated sodium chloride solution (250 mL) was added, and the solution was washed with diethyl ether (100 mL). The aqueous layer was acidified with sulfuric acid (200 mL, 1 M) to precipitate the product, which was collected and recrystallized from toluene to give methyl 2-hydroxy-4-oxo-6-phenylcyclohex-2-en-1-oate (**5c**, 52 g, 82%): mp and mixed mp with a sample prepared by Method 1 were undepressed (159–161 °C).

Methyl 6,6-Dimethyl-2-hydroxy-4-oxocyclohex-2-en-1-oate (5d)—The desired compound, **5d**, was obtained according to literature procedures[5,10] in a yield of 77 g (78%): mp 100–102 °C (from toluene) (Lit.[10] mp 102 °C); ^{1}H NMR ($CDCl_3$): δ 1.05 (s, 6H, 2 × CH_3), 2.35 (AB system, 2H, CH_2), 3.10 (s, 1H, CH), 3.65 (s, 3H, OCH_3), 5.45 (s, 1H, =CH), 9.35 (s, 1H, OH).

Diethyl 2-(3-Oxobutyl)malonate (7b)—To a mixture of diethyl malonate (**6**, 80 g, 0.5 mol) and anhydrous potassium carbonate (6 g, 43 mmol) was added methyl vinyl ketone (**3a**, 35 g, 0.5 mol) with stirring. The reaction mixture was kept at 40–50 °C for 3 h, cooled, and neutralized with hydrochloric acid (60 mL, 2.5 M). The organic layer was separated, dried over anhydrous magnesium sulfate, and distilled to provide diethyl 2-(3-oxobutyl)malonate (**7b**, 85 g, 74%): bp 188–192 °C, 20 mbar (Lit.[2] bp 131 °C, 3 mbar); IR (neat): ν 2980 (CH), 1740 (C=O), 1720 (C=O), 1362 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.25 (t, 6H, J = 7 Hz, 2 × CH_3 of C_2H_5), 2.10 (s, 3H, CH_3), 2.20 (m, 4H, 2 × CH_2), 3.35 (t, 1H, J = 6 Hz, CH), 4.15 (q, 4H, J = 7 Hz, 2 × CH_2 of C_2H_5).

Dimethyl 2-(3-Oxobutyl)malonate (7a) and Dimethyl 2,2-Bis-(3-oxobutyl)malonate (9a)—A similar procedure as for **7b** provided dimethyl 2-(3-oxobutyl)malonate (**7a**, 80%): bp 50–53 °C, 0.5 mbar; IR (neat): 2950 (CH), 1740 (C=O), 1720 (C=O), 1440 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.10 (s, 3H, CH_3), 2.05 (m, 5H, 2 × CH_2 + CH), 3.70 (s, 6H, 2 × OCH_3).

The second fraction (bp 100–140 °C, 1 mbar) gave dimethyl 2,2-bis-(3-oxobutyl)malonate **9a** (16%): mp 79–80 °C (from ethanol); IR (neat): ν 3000, 2950 (CH), 1740 (C=O), 1720 (C=O), 1440 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.20 (m, 8H, 4 × CH_2), 2.10 (s, 6H, 2 × CH_3), 3.70 (s, 6H, 2 × OCH_3).

Anal.—Calcd ($C_{13}H_{20}O_6$) C, H.

Ethyl 2-Hydroxy-4-oxocyclohex-2-en-1-oate (8b)—A similar procedure as described for **5a** gave ethyl 2-hydroxy-4-oxocyclohex-2-en-1-oate (**8b**, 63%): mp 60–62 °C (from toluene) (Lit.[4] mp 62.5 °C); mp and mixed mp 60–62 °C were undepressed on admixture with an authentic sample.

2-Hydroxy-4-oxo-6-methylbicyclo[3.3.1]nona-2,6-dien-1-oic Acid (10)—To a freshly prepared solution of sodium (13.4 g, 0.6 g-atom) in methanol (160 mL) was added **9a** (121 g, 0.4 mol) with constant stirring on an ice bath. The reaction mixture was refluxed for 1 h during which a white precipitate formed and impeded stirring. The magnetic stirrer was replaced with a mechanical stirrer, and the reaction mixture was refluxed for a further 4 h, cooled, acidified with sulfuric acid (300 mL, 1 M), and extracted with dichloromethane (2 × 400 mL). The organic phase was dried over anhydrous magnesium sulfate, evaporated, and crystallized from diethyl ether to give 2-hydroxy-4-oxo-6-methylbicyclo-[3.3.1]nona-2,6-dien-1-oic acid (**10**, 29 g, 14%): mp 188–190 °C dec (butanone) (Lit.[4] mp 190–191 °C); IR (KBr): ν 3000 (br OH), 1710 (C=O), 1630, 1570, 1300 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 1.75 (s, 3H, CH_3), 2.50 (m, 5H, 2 × CH_2 + CH), 5.21 (s, 1H, =CH), 5.47 (s, 1H, =CH), 11.73 (b s, 2H, 2 × OH).

Anticonvulsant Evaluation—The evaluation of compounds for anticonvulsant activity was performed in male Carworth Farms #1 (CF1) mice in three tests: maximal electroshock (MES), subcutaneous pentylenetetrazol (scMet), and rotorod neurological toxicity (Tox) by intraperitoneal injection at three dosage levels (30, 100, and 300 mg/kg).[6]

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