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Investigation in the Dipropylacetic Acid Series, C_8 and C_9 Branched Chain Ethylenic Acids and Amides

(Eingegangen am 24. Juni 1976)

2-Propyl-2-pentenoic acid was prepared. Its stereochemistry was determined using the A.S.I.S.-effect. The dehalogenation by *N,N*-diethylaniline of some *N*-substituted 2-bromo-2,2-dipropylacetamides gave the corresponding unsaturated amides. The configurations of these compounds are discussed on the basis of NMR data obtained with and without complexation with tris(dipivaloylmethano)europium [Eu $(DPM)_3$].

Untersuchungen in der Dipropylessigsäure-Reihe, C_8 und C_9 verzweigtkettige Olefincarbonsäuren und davon abgeleitete Amide

2-Propyl-2-pentensäure wurde synthetisiert und mit Hilfe des A.S.I.S.-Effektes ihre Stereochemie bestimmt. Die Dehalogenierung einiger N-substituierter 2-Brom-dipropylacetamide ergibt die entsprechenden ungesättigten Amide. Aufgrund der NMR-Spektren mit und ohne Komplexierung mit Eu(DPM_3) wird die Z- oder E-Konfiguration dieser Verbindungen diskutiert.

Since we first reported its activity, we made several modifications upon the dipropylacetic acid (DPA) structure. On the one hand we tried to obtain better anticonvulsant properties, and on the other hand to develop some other neurotropic activities of the prototype[1]. We must bear in mind that DPA induces a competitive inhibition of GABA-transaminase against its substrate, the 4-amino-butyric acid[2].

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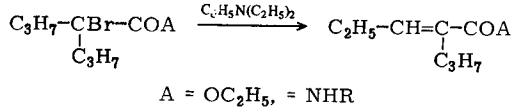
1 G. Carraz, A. Boucherle, S. Lebreton and M. Boitard, Therapie *19*, 917 (1964).

2 S. Simler, L. Ciesielski, M. Maitre, H. Randrianarisoa and P. Mandel, Biochem. Pharmacol *22*, 1701 (1973).

In the beginning, we prepared amides and esters[3]. Then we replaced the carboxyl by an amine function that was either directly fixed at the carbon atom bearing the two propyl groups[4], or fixed by means of a linear or a branched chain[5][6].

In this present work, we reverted to structures more closely related to dipropylacetic acid or homologous dipropylpropionic acid(3-propyl hexanoic acid), but we introduced a double bond α, β or β, γ to the carboxyl. From N,N-diethylaniline dehalogenation of 2-bromo-2-propyl-valeric acid, we succeeded in isolating 2-propyl-2-pentenoic acid and a few amides.



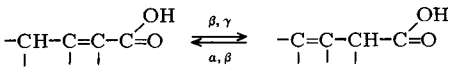
A = OC_2H_5, = NHR

We obtained 3-propyl-2-hexenoic acid and two unsaturated amides, 3-propyl-2-hexenamide and 3-propyl-3-hexenamide, from 3-hydroxy-3-propyl-hexanoic acid. The position of the double bond of each molecule has been ascertained by spectral data. Furthermore if the stereoisomerism of a molecule was not unique we tried to precise its configuration.

This work has been completed by some pharmacological data.

I – 2-Propyl-2-pentenoic Acids and Amides

It has been reported that α, β ethylenic acid preparation is difficult because of the ability of the double bond to migrate. The unit responsible for tautomerism bears at its end a carboxyl with an electronegative oxygen atom and isomerisation occurs through a prototropic mechanism. It leads to an equilibrium between α, β and β, γ unsaturated acids.



This equilibrium has been studied by *Kon* and *Linstead.* The main results have been recollected and summed up by *Ingold*[7].

The separation of α, β from β, γ unsaturated acids is difficult indeed but it is even much more so when in addition Z and E or S-cis and S-trans stereoisomers

3 J. L. Benoit-Guyod, A. Boucherle and G. Carraz, Bull. Soc. Chim. Fr. *1965,* 1660.

4 M. Benoit-Guyod, J. L. Benoit-Guyod, A. Boucherle, M. Broll and P. Eymard, Chim. Ther. *5,* 388 (1972).

5 M. Benoit-Guyod, J. L. Benoit-Guyod, A. Boucherle, M. Broll and P. Eymard, Chim. Ther. *5,* 393 (1972).

6 M. and J. L. Benoit-Guyod, A. Boucherle, M. Broll and P. Eymard, Chim. Ther. *4,* 412 (1973)

7 C. K. Ingold, Structure and Mechanism in organic chemistry, second edition, p. 823, G. Bell and sons Ltd., London 1969.

have to be considered. The literature seldom gives any precise statements on the stereochemistry of α, β or β, γ unsaturated acids or of their derivatives.

After dehydration of 2-propyl-2-hydroxy-valeric acid, *Blaise* and *Bagard*[8] get an "unstable" and liquid 2-propyl-2-pentenoic acid ($bp_8 = 116°$). They prepare anilide (m. p. = 40–41°) and β-naphtylamide (m. p. = 104°). 2-Bromo-2-propyl-pentanoic acid ethyl ester (or 2-bromo-2-propyl-valeric acid ethyl ester) treated by N,N-diethylaniline and further saponification gives a "stable" 2-propyl-2-pentenoic acid as a solid (m. p. = 36°) out of which they get acid chloride ($b.p._9 = 74°$), anilide (m. p. = 68°), β-naphtylamide (m. p. = 89°) and ethyl ester ($b.p._{10} = 83°$). They propose no configuration for the stable and unstable forms. Nor did *Macq*[9] for the two amide isomers he obtained (m. p. = 89° and m. p. = 115,5°). *Morgan*[10] obtained an exclusively at 115° melting amide isomer by reaction of ammonia on the acid chloride. On the contrary, *Wheeler* and Coworkers[11] when heating 2-bromo-2-propyl-valeramide at 130–140° with N,N-diethylaniline, get the isomeric mixture. They separate two fractions m.p. = 72° and m.p. = 86°. Recently *Neuman* and Coworkers[12] prepared both acids. They claim that the higher boiling isomer has trans configuration.

1) 2-Propyl-2-pentenoic Acid

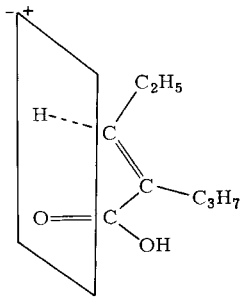
We used the method of *Blaise* and *Bagard:* 2-bromo-2-propyl-valeric acid ethyl ester was treated by N,N-diethylaniline; saponification then gave the 36° melting isomer.

NMR study of this compound ascertains that the double bond is located exclusively in the α, β position (a triplet around 6,88 ppm and no quadruplet). The high value of the coupling constant of the ethylenic proton (13 Hz) seems to show that 2-propyl-2-pentenoic acid has E configuration. We applied the A.S.I.S. effect (Aromatic Solvent Induced Shift) upon 2-propyl-2-pentenoic acid. It was first used on ketones by *Connolly* and *Mc Grindle*[13] and enables one to locate a proton neighbouring a carboxyl group. The authors define a model in which the reference plane passes through the C atom of the carbonyl group while remaining perpendicular to the axis of the orbital of the C = O bond. If the results of *Timmons*[14] about α, β-unsaturated ketones are transposed to α, β unsaturated acids, the A.S.I.S. effect should give the following results: – The shift should be widely different from zero for every proton far from the plane. It is positive when the proton is behind and negative when it is in front of the plane, as is the oxygen of C = O group (E, s-trans form). – Chemical shift of the ethylenic proton:

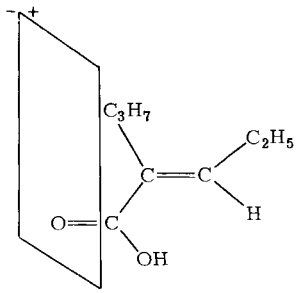
$$\Delta\delta_{(H)} = \delta_{(H)}\ CDCl_3 - \delta_{(H)}\ C_6D_6$$

is expected to be practically zero if the proton is situated on the reference plane (E, s-cis form).

8 E. Blaise and P. Bagard, Ann. Chim. (Paris) 8, *11,* 111 (1907).
9 A. Macq, Bull. Sci. Acad. Roy. Belg. (5), *12,* 753 (1926).
10 E. D. Morgan and N. Polgar, J. Chem. Soc. *1958,* 4077.
11 K. W. Wheeler, M. G. Van Campen Jr. and R. S. Shelton, J. Org. Chem. *25,* 1021 (1960).
12 R. C. Neuman Jr. and G. D. Holmes, J. Am. Chem. Soc. *93,* 4242 (1971).
13 J. D. Connolly and R. Mc Grindle, Chem. Ind. (London), *1965,* 3179.
14 C. J. Timmons, Chem. Commun. *22,* 576 (1965).



E, s cis



E, s trans

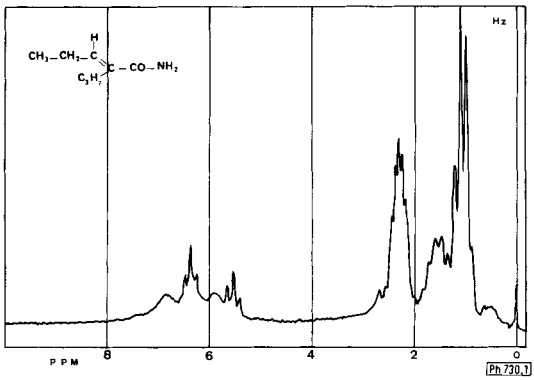
The A.S.I.S. effect is measured according to the difference between the chemical shift in hexadeuterated benzene in relation to deuterated chloroform. For the ethylenic proton:
$\Delta\delta_{(H)} = \delta_{(H)}\ CDCl_3 - \delta_{(H)}\ C_6D_6 = 6{,}88-6{,}94 = -0{,}06$ ppm

Similarly, for the CH_2 protons of the propyl group in α position of the double bond:
$\Delta\delta_{(CH_2)} = \delta_{(CH_2)}\ CDCl_3 - \delta_{(CH_2)}\ C_6D_6 = 2{,}2-1{,}9 = +0{,}3$ ppm

Thus 2-propyl-2-pentenoic acid should have the E,S-cis configuration.

2) 2-Propyl-2-pentenamides

They have been prepared from the corresponding α-bromo amides. A hydrogen bromide molecule is eliminated by heating with N,N-diethylaniline. The results will be found in table III. Since the purification of α-bromo amides is difficult, we used the crude products after a single purification out of hot hexane. 2-Propyl-2-pentenanilide was prepared in a different way, from E 2-propyl-2-pentenoic acid via the chloride.



N.M.R. spectrum of 2-propyl-2-pentenamide in $CDCl_3$

Configuration

The NMR spectra in deuterated chloroform show no quadruplet. The molecules are effectively α, β-ethylenic amides.

The different spectra show either one or two triplets at 5,30–5,50 ppm and 6,25–6,30 ppm. When there are two triplets it seems to be a mixture of Z and E forms.

We tried to obtain clues on the configuration of these molecules through the A.S.I.S. effect. No valuable data were obtained because both deuterated chloroform and hexadeuterated benzene give the same type of signals.

Table I:

Amides: C_2H_5-CH = C(-C_3H_7)-CONHR

R	δ = CH			δ = CH		
	$CDCl_3$	C_6D_6	Δ	$CDCl_3$	C_6D_6	Δ
H	5,45	5,25	0,20	6,30	6,10	0,20
$C(-CH_3)_3$	5,30					
C_6H_{11}	5,35	5,25	0,10			
C_6H_5				6,25	6,10	0,15
$C_6H_4Cl_{(4)}$	5,50	5,25	0,25	6,25	6,00	0,25

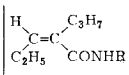
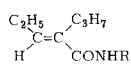
Then, we tried to use another method. It has been shown that chelates of rare earth metals, induct strong paramagnetic shifts in the NMR spectra of molecules with a pair of electrons on a functional group; the value of the shift allows localisation of the functional group or determination of the configuration[15]. Tris-dipivaloyl-methano europium ($Eu(DPM_3)$) is a very efficient reagent for the determination of the Z-E configuration of α, βethylenic compounds (alcohols, aldehydes, amines, amides)[16].

The NMR spectrum of 2-propyl-2-pentenamide was made with $Eu(DPM)_3$ in deuterated benzene. We studied the shift of both triplets. The higher field triplet shifts towards lower field from 6,15–5,45 = 0,70 ppm. The lower field triplet from 8,10–6,30 = 1,80 ppm. The lower field triplet shifts farther than the higher one. The same result is obtained with 2-propyl-2-pen-

15 J. P. Begue, Bull. Soc. Chim. Fr. *5*, 2073 (1972).

16 G. Montaudo, V. Librando, S. Caccamese and P. Maravigna, J. Am. Chem. Soc. *95*, 6365 (1973).

tene-(4'-chlor-anilide). This triplet should be due to the E form. Appointment of configuration and the percentage of isomers of each amide have been reckoned according to that result.

R		
	Z%	E%
H	50	50
$C(-CH_3)_3$	100	0
C_6H_{11}	100	0
C_6H_5	0	100
$C_6H_4Cl_{(4)}$	80	20

We can conclude that the α-bromo amides treated by N,N-diethylaniline, give α, β-ethylenic amides, – either a mixture of Z and E isomers – or the Z isomer alone. The only E ethylenic amide obtained in a pure form has been prepared from E ethylenic acid. This acid was prepared by heating the corresponding α-bromo ester with N,N-diethylaniline followed by saponification. The reaction mechanism should be the same as for the amides and thus an isomerous mixture of Z and E form should appear. In fact, a small part only of the crude saponification mixture cristallizes with petroleum ether and thus gives E acid. The remaining liquid may be constituted of Z α, β-ethylenic acid and possibly mixed to a certain amount of β, γ-ethylenic acid. We did not try to determine the composition of this fraction.

II – Ethylenic Acids and Amides from 3-Hydroxy-3-propyl-Hexanoic Acid

3-Hydroxy-3-propyl-hexanoic acid is obtained according to the method of *Angelo*[17]; the 4-heptanone is condensed with acetic acid by means of the complex prepared from lithium reacting on naphtalene in THF.

From the mixture of isomerous ethylenic acids obtained after dehydration of the above β-hydroxy-acid, we were able to isolate 3-propyl-2-hexenoic acid. The NMR spectrum has neither singulet nor quadruplet corresponding to an A–B system which would have indicated the presence of a CH_2-COOH. The acid is then effectively the α, β-ethylenic acid. Furthermore it has a non coupled ethylenic proton at 5,65 ppm.

From the same mixture of isomerous acids we prepared the amides and resolved the mixture. We got 3-propyl-2-hexenamide with an ethylenic proton singulet at 5,6 ppm and 3-propyl-3-hexenamide with an ethylenic proton triplet at 5,35 ppm.

III – Pharmacological Data

None of the compounds showed any toxic effects with the used doses. The activity of the compounds was tried upon Cardiazol® crisis.

17 B. Angelo, Bull. Soc. Chim. Fr. *5*, 1848 (1970).

The α, β or β, γ double bond does not affect activity. A dose of 0,9 mmol/kg of 2-propyl-2-pentenoic acid gives a 65 % protection against Cardiazol (DPA 70 %). Protection is no more than 45 % with the same dose of 3-propyl-2-hexenoic acid (dipropylacrylic acid) while the saturated homologous 3-propyl-hexanoic acid (dipropylpropionic) gives a 100 % protection. 2-Propyl-2-pentenamides loose all their anticardiazol activity when the nitrogen is substituted, as in the case of the dipropylacetamides.

The pharmacological spectrum of 3-propyl-3-hexenamide looks much like Depamide® spectrum (anticonvulsant activity, ptosis inhibition, and reserpinic catatony inhibition) though not so strong, 1,3 mmol/kg is needed to reach a 90 % protection against Cardiazol® crisis. The protection falls down to 30 % at 0,65 mmol/kg. 3-Propyl-2-hexenamide is more active than DPA against the Cardiazol® crisis. Unlike DPA, it has no effect on intraperitoneal allylglycine convulsions. It has been reported that this type of convulsion is inducted by GABA level fall. Other compounds have not been tested upon allylglycine convulsions.

3-Propyl-2-hexenamide is a mild hypnotic. A 200 mg/kg (1,3 mmol.) intraperitoneal dosis gives after 20 min 100 % of a 80 minutes' sleep. But per os, the activity is much weaker: after 9 min, 35 % of 29 min lasting sleep.

Experimental Section

I. Chemistry

Melting points: in capillary tubes either on a FP1 Mettler or on a Gallenkamp melting point apparatus. *IR spectra:* IR 8 Beckman, using potassium bromide pills; *NMR spectra:* Hitachi Perkin Elmer R 24 (60 MHz), exept when otherwise stated in $CDCl_3$-solution; *UV spectra:* SP 800 Unicam in ethanolic solution.

1) *2-Propyl-2-pentenoic acid*

50,2 g (0,20 mol) of 2-bromo-2-propyl-pentanoic acid ethyl ester are refluxed for 2 h with 80 g (0,54 mol) of N,N-diethylaniline. After cooling, the mixture partly cristallizes. The liquid phase is distilled under reduced pressure (15 mm Hg). The fraction boiling up to 70–90° is collected, washed with 10 % sulfuric acid and extracted with ether. The etheral extracts are washed and dried. After removal of the ether, the residue is distilled.

The yield is 26,5 g of 2-propyl-2-pentenoic acid ethyl ester (76,5 %) $bp_{0,07}$ = 36–38° Lit.[8] bp_8 = 76–77°.

25,5 g of ester (0,15 mol) are refluxed for 2 h with 9 g of soda (0,225 mol), 50 ml water and 25 ml ethanol. The mixture is brought to acid reaction with slow addition of 10 % sulfuric acid thereby avoiding any heating. After cooling the solution is extracted with ether. The ether extracts are washed, dried and evaporated to dryness. The residue is olved in petroleum ether and kept at −20°. The acid crystallizes and is purified by repeated recrystallizations out of petroleum ether. The yield is 7,1 g (25 %) of the bromo acid ester. mp = 34,5°, lit.[8] = 36°; UV: λ max = 218 nm; IR: $\nu_{C=O}$ = 1660, $\nu_{C=C}$ = 1615 cm^{-1}.
$C_8H_{14}O_2$ (142,2) Calc.: C 67,57 H 9,92; Found: C 67,81 H 10,09.

2) *2-Propyl-2-pentenamides*

a) 2-Bromo-2-propyl-pentanamides

These have been used crude after a single purification. We describe as an example the synthesis of N-cyclohexyl-2-bromo-2-propyl-pentanamide. 14,3 g of 2-bromo-2-propyl-pentanoic acid bromide (0,05 mol) are refluxed with 9,9 g of cyclohexylamine (0,1 mol) and 50 ml of anhydrous benzene. The mixture is washed, dried and evaporated to dryness. The residue is washed with petroleum ether and purified from hexane.

b) Unsaturated amides

We describe as an example the synthesis of 2-propyl-2-pentene-(4'chloro-anilide). 4,15 g of 2-bromo-2-propyl-pentane-(4'-chloroanilide) (0,0125 mol) are kept for 2 h under reflux with 12 g of N,N-diethylaniline. After cooling 30 ml ether are added: the organic phase is collected, washed with 10 % H_2SO_4 to give acid reaction with litmus, carefully washed with water, dried and evaporated. The residue is purified from hexane. The other amides have been prepared using the same procedure, but the yields were always low (20 %). The 2-propyl-2-penten-anilide is prepared in a different way, from 2-propyl-2-pentenoic acid.

3) *3-Hydroxy-3-propyl-hexanoic acid derivatives*

a) 3-Hydroxy-3-propyl-hexanoic acid

1 mol of naphtalene (128 g), 1 equiv. of Li (7 g) and 600 ml of anhydrous tetrahydrofuran are stirred for 3 or 4 h under nitrogen. To the mixture cooled to $-10/-15°$, a solution of 0,5 mol (30 g) of acetic acid in its volume of THF is added dropwise followed by heating for 90 min at 50–60°. A solution of 0,5 mol of 4-heptanone (57 g) in 250 ml of ether is rapidly added to the reaction mixture. The mixture is then refluxed for 90 more min. After hydrolysis with a minimum amount of water, the alcaline layer is separated, acidified and extracted with ether. The ether solution is dried, filtered, evaporated and distilled. $bp_{0,25}$ = 108–110°, yield = 59 %.
$C_9H_{18}O_3$ (174,24) Calc. C 62,04 H 10,41; Found: C 62,15 H 10,40

b) 3-Propyl-2-hexenoic acid

3-Hydroxy-3-propyl-hexanoic acid is refluxed for 2 h/2 h 30 min with acetic acid anhydride (1 g of acid versus 5 g of anhydride). After evaporation of acetic acid anhydride and acid the mixture of the isomeric ethylenic acids is distilled. Pure 3-propyl-2-hexenoic acid (or dipropylacrylic acid) is isolated by cooling to $-30/-40°$, the fraction of isomeric ethylenic acids boiling at 110° under 0,6 mm. The crystallized acid is quickly filtered and washed with cooled petroleum ether.
Yield 5 %; mp = 20°, lit[18]: 8°; IR: $\nu_{C=O}$ = 1650, $\nu_{C=C}$ = 1600 cm^{-1}.
NMR: a non coupled ethylenic proton at 5,65 ppm, 3 t at 0,95 ppm (6 H), 2,2 ppm (2 H), 2,6 ppm (2 H) and a sext at 1,5 ppm (4 H).
$C_9H_{16}O_2$ (156,227) Calc.: C 69,19 H 10,32; Found: C 69,43 H 10,31.

c) 3-Propyl-2-hexenamide

The previouly mentioned mixture of isomeric ethylenic acids is first converted into the acid chlorides, then into the corresponding amides. The E amide is recrystallized out of petroleum ether (fraction bp = 110–120°). Yield 15 %; mp = 72°, I.R. = $\nu_{C=O}$ = 1650, $\nu_{C=C}$ = 1600, $\nu_{NH\ sym}$ = 3160, $\nu_{NH\ asym}$ = 3350 cm^{-1};
UV: λ_{max} = 221 nm.

Table III: Amides C_2H_5-CH = C(-C_3H_7) – CONH-R

R	m.p.	Crist. solv.	U.V. (nm) λmax λ'max	I.R. (cm^{-1}) γ NH bands in the 1600–1650 cm^{-1} region			M	Analysis					
								C %		H %		N %	
								calc.	found	calc.	found	calc.	found
H	85	Hexane	214	asym 3380 sym 3180	1640	1660	$C_8H_{15}NO$ (141,216)	68,04	68,26	10,70	10,75	9,92	9,68
$C(-CH_3)_3$	53,5	Hexane	208	3270	1620	1640	$C_{12}H_{23}NO$ (197,324)	73,04	72,81	11,75	11,85	7,10	7,30
C_6H_{11}	136	Octane	208	3260	1615	1650	$C_{14}H_{25}NO$ (223,362)	75,28	75,15	11,28	11,13	6,27	6,47
C_6H_5	71,5	Hexane	214 256	3265	1600	1635 1660	$C_{14}H_{19}NO$ (217,314)	77,37	77,46	8,81	8,58	6,44	6,40
$C_6H_4Cl_{(4)}$	117	Hexane	207 253	3270	1650		$C_{14}H_{18}ClNO$ (251,763)	66,79	66,99	7,20	7,25	5,56	5,53

NMR: 3 t at 0,9 ppm, 2,05 ppm and 2,63 ppm. 1 sext at 1,45 ppm. The ethylenic proton appears at 5,6 ppm and the NH_2 protons at 6 ppm.
$C_9H_{17}NO$ (155,243) Calc.: C 69,63 H 11,04 N 9,02; Found: C 69,54 H 11,03 N 9,06.

d) 3-Propyl-3-hexenamide

3-Hydroxy-3-propyl-hexanoic acid is dehydrated by distillation under reduced pressure (15 torr). The mixture of the ethylenic acids is treated with thionyl chloride and then transformed into a mixture of the corresponding amides. The desired amide is isolated and purified after several recrystallizations from octane-benzene. Yield: 10 %; mp = 119–120°, Lit.[18]: 120–121°; IR: $\nu_{C=O}$ = 1650, $\nu_{C=C}$ = 1612, $\nu_{NH\ sym}$ = 3190, $\nu_{NH\ asym}$ = 3360 cm^{-1}. UV: λ_{max} = 207 nm
NMR: ethylenic proton gives a t. at 5,35 ppm.
$C_9H_{17}NO$ (155,243) Calc.: C 69,63 H 11,04; Found: C 69,56 H 11,09.

II. Pharmacology

The tests have been made on male OF_1 mice, weighting 20–25 g. The drugs were given in an olive oil suspension.

The anticonvulsant activity has been studied on pentetrazol crisis. Pentetrazol (125 mg/kg I.P.) was injected IP 15 min. after the studied drug. The reference was dipropylacetic acid (DPA) and dipropylacetamide.

18 G. A. R. Kon and C. J. May, J. Chem. Soc. *129*, 1549 (1927).

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