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Substances Acting on the Central Nervous System. III.* Synthesis of the Racemic and Optically Active 2-Ethyl-2-phenylglutarimide***

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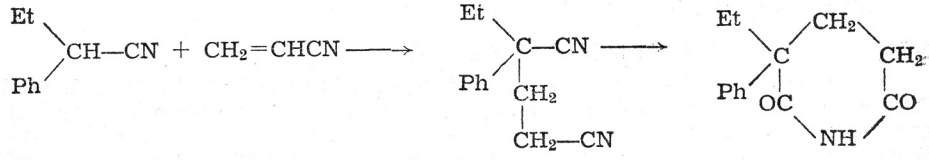
Condensation of 2-phenylbutyronitrile with acrylonitrile gave 2-ethyl-2-phenylglutaric acid dinitrile which was cyclisized to 2-ethyl-2-phenylglutarimide. 2-Ethyl-2-phenylglutaric acid mononitrile was resolved with brucine or cinchonidine into optical antipodes which were converted into the corresponding isomers of 2 - ethyl-2-phenylglutarimide and 2 - ethyl - 2 - phenylglutaric acid monoamide.

It has been known that 2-ethyl-2-phenylglutarimide (III) is a central nervous system depressant, hypnotic and sedative. Two syntheses for this compound were described starting either from 2-ethyl-2-phenylglutaric acid mononitrile (IV) or from the ethyl ester of this acid[1,2]. These intermediates were prepared by condensation of 2-phenylbutyronitrile (I) with ethyl β-bromopropionate and methyl acrylate respectively.

The present paper describes a more economical synthesis of III starting from acrylonitrile which is much cheaper than ethyl β-bromopropionate and methyl acrylate. In this way the hitherto undescribed 2-ethyl-2-phenylglutaric acid dinitrile (II) was prepared. This dinitrile was cyclisized according to the procedure reported by Hoffmann *et al.*[2] into 2-ethyl-2-phenylglutarimide (III).



I II III

The preparation of two optically active isomers of III was undertaken, because it was thought that one enantiomorph might be physiologically more active, as in the case of other biologically active substances[3-11]. The optical antipodes of III, (VII and VIII) have been prepared by heating V and VI

* Paper II, Lj. Polak and S. Kukolja, *Croat. Chem. Acta* **32** (1960) 151.

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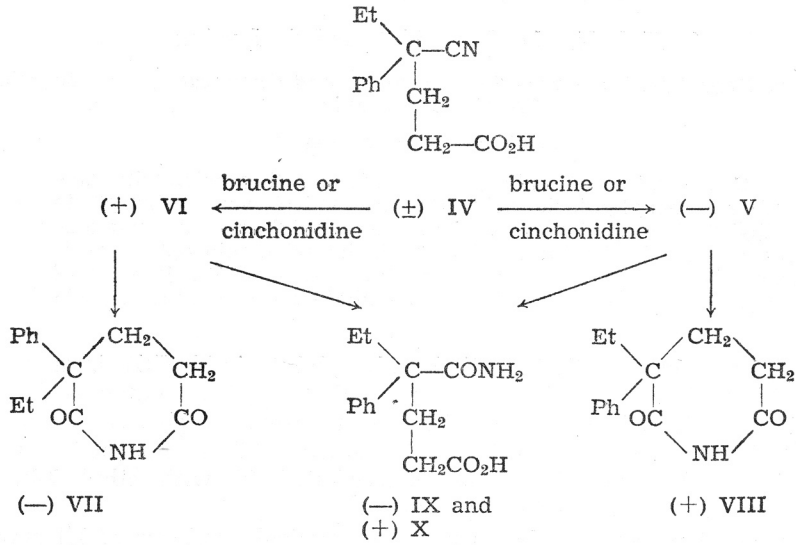
*** *Note added in Proof.* — R. Branchini, G. Casini, M. Ferappi, and S. Gullinelli have recently published a paper [*Farmaco, Pavia, Ed. Sci.*, **15** (1960) 734] dealing with the optical antipodes of 2-ethyl-2-phenylglutarimide.

with 85% sulphuric acid in acetic acid during 10 minutes. When V or VI were treated with 85% sulphuric acid for 20—30 seconds they gave the corresponding monoamides IX and X.

2-Ethyl-2-phenylglutaric acid mononitrile (IV) was resolved by fractional crystallization of the appropriate brucine or cinchonidine salts from dilute ethanol. Both the brucine and the cinchonidine salt of the laevorotatory acid (VI) were less soluble in dilute ethanol and could be isolated in the optically pure state by repeated crystallization.



(—) VII (—) IX and (+) X (+) VIII

The dextrorotatory acid VI was isolated from the combined mother liquors. Both V and VI were oily compounds, while the racemic acid IV was solid.

EXPERIMENTAL

All melting and boiling points are uncorrected.

2-Ethyl-2-phenylglutaric acid dinitrile (III)

To a solution of 290 g. (2 moles) of 2-phenylbutyronitrile in 500 ml. of dry dioxane were simultaneously added during one hour at 20—32° 160 ml. (2.4 moles) of acrylonitrile and 50 ml. of a 50% solution of Triton B[12,13] dropwise with stirring. When the addition was complete the mixture was heated for one hour at 75—80°. The dioxane was removed *in vacuo* and the residue was taken up in benzene, washed with water and dried with anhyd. sodium sulphate. The solvent was removed and the residue distilled under reduced pressure. The product distilled at 140—142° /1 mm., yield 334 g. (84%). The analytical sample was distilled on the Widmer column and the fraction distilling at 127.5—131°/0.75 mm. had n_D^{25} 1.5159 and d_4^{25} 1.1037.

Anal. $C_{13}H_{14}N_2$ (198.26) calc'd.: C 78.75; H 7.12; N 14.13%
found : C 78.52; H 7.02; N 14.03%

Racemic 2-ethyl-2-phenylglutarimide (III)

A mixture of 59.5 g. (0.3 mole) of 2-ethyl-2-phenylglutaric acid dinitrile, 104 ml. of acetic acid and 50 ml. of 85% sulphuric acid was heated on a water bath for 4 hours. The acetic acid was removed at the water-pump and the oily residue was dissolved in 100 ml. of benzene and 40 ml. of water. The benzene extract was

washed twice with dilute sodium bicarbonate, then with water and dried with anhyd. sodium sulphate. After removing the solvent a dark-coloured viscous oil residue solidified on cooling. It was crystallized from *i*-propanol, yielding 40 g. (62%) with m. p. 82—83°. An authentic specimen of III melts at 82—84°, no depression was found with a mixed sample.

(—)-2-Ethyl-2-phenylglutaric acid mononitrile (V)

110 g. (0.507 mole) of racemic 2-ethyl-2-phenylglutaric acid mononitrile[1] and 200 g. of brucine were dissolved in 800 ml. of hot 48% ethanol. The solution was allowed to cool and left to crystallize overnight in a refrigerator. The precipitate was filtered off, and after drying weighed 168 g. After six recrystallizations from 48% ethanol 95 g. of the brucine salt was obtained, which was decomposed with 2 *M* sulphuric acid. The organic acid was extracted with ether. After the ether was removed a pale yellow oil remained. The yield of crude acid was 26.6 g. $[\alpha]_D^{20}$ —25.6° (c, 2.17 in methanol). The analytical sample was a colourless oil distilling at 155—156°/0.46 mm., d_4^{20} 1.5253 and showed $[\alpha]_{20}^{D}$ —21.2° (c, 0.992 in methanol).

Anal. $C_{13}H_{15}O_2N$ (217.26) calc'd.: C 71.86; H 6.96; N 6.45%
found: C 71.91; H 6.55; N 6.36%

Similar results were obtained with cinchonidine.

(+)-2-Ethyl-2-phenylglutaric acid mononitrile (VI)

The mother liquors from all six crystallizations of the brucine, respectively cinchonidine salt, were combined and evaporated to dryness at room temperature *in vacuo*. The acid was liberated from the residue (207 g.) with 2 *M* sulphuric acid and extracted with ether. The ether extract was washed with water and dried over anhyd. sodium sulphate. After the solvent was removed, a semi-crystalline mass remained, which consisted of a mixture of the (+) isomer V and the racemic acid IV. The oily dextrorotatory isomer was separated from the solid racemic acid by suction. The yield of crude acid was 10 g. $[\alpha]_D^{20}$ +23.7° (c, 1.36 in methanol). The analytical sample was distilled at 175—190° (bath temp.) and 0.5 mm.

Anal. $C_{13}H_{15}O_2N$ (217.26) calc'd.: C 71.86; H 6.96; N 6.45%
found : C 71.86; H 7.11; N 6.89%

(+)-2-Ethyl-2-phenylglutarimide (VIII)

VIII was prepared from 2-ethyl-2-phenylglutaric acid mononitrile (10.2 g.) as described for the racemate[2]. Yield 6.5 g. (63%). A sample for analysis was crystallized twice from *i*-propanol and showed the m. p. 102.5—103° and $[\alpha]_D^{20}$ +176° ± 2° (c, 1.0 in methanol).

Anal. $C_{13}H_{15}O_2N$ (217.26) calc'd.: C 71.86; H 6.96; N 6.45%
found : C 71.75; H 6.73; N 6.69%

(—)-2-Ethyl-2-phenylglutarimide (VII)

The laevoratotory imide (VII) was prepared from VI in an analogous manner. M. p. 102—103°, $[\alpha]_D^{20}$ —181° ± 2° (c, 1.0 in methanol).

Anal. $C_{13}H_{15}O_2N$ (217.26) calc'd.: C 71.86; H 6.96; N 6.45%
found : C 71.85; H 6.85; N 6.68%

(—)-2-Ethyl-2-phenylglutaric acid monoamide (IX)

A mixture of 1.1 g. of (—) 2-ethyl-2-phenylglutaric acid mononitrile and 5.2 ml. of 85% sulphuric acid was heated during 20—30 seconds. The reaction product was poured into 25 ml. of cold water. The amide was then filtered off, washed with water, dissolved in a mixture of 6 ml. ether and 10 ml. of a saturated solution of sodium bicarbonate. The sodium bicarbonate solution was acidified and the oily

product extracted with ether. The extract was washed with dild. hydrochloric acid, then with water and dried. The ether was evaporated and the residue crystallized from 30% ethanol (yield 0.9 g., 76.4%). It forms colourless crystals m.p. 176—177°; $[\alpha]_D^{20}$ —15.4° (c, 0.41 in MeOH), soluble in alcohol and acetic acid, insoluble in water and ether.

Anal. $C_{13}H_{17}O_3N$ (235.27) calc'd.: C 66.36; H 7.28; N 5,95%
found: C 66.21; H 7.17; N 6.25%

(+)-2-Ethyl-2-phenylglutaric acid monoamide (X)

X was prepared from 1 g (+)-2-ethyl-2-phenylglutaric acid mononitrile as described above for the (—) antipode. Yield 0.8 g. (74%). For analysis the sample was recrystallized twice from 30% ethanol, m.p. 176—177°, $[\alpha]_D^{20}$ + 9.2° (c, 0.41 in MeOH).

Anal. $C_{13}H_{17}O_3N$ (235.27) calc'd.: C 66.36; H 7.28; N 5.95%
found: C 66.28; H 6.96; N 6.19%

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IZVOD

Supstance koje djeluju na centralni nervni sistem. III. Sinteza racemičnog 2-etil-2-fenilglutarimida i optički aktivnih antipoda

S. Kukolja, D. Grgurić i L. Lopina

Kondenzacijom 2-fenilbutironitrila s akrilonitrilom pripravljen je dinitril 2-etil-2-fenilglutarne kiseline, i dalje ciklizacijom preveden u 2-etil-2-fenilglutarimid. Mononitril 2-etil-2-fenilglutarne kiseline cijepan je s brucinom i cinhonidinom u optičke antipode, koji su zatim prevedeni u odgovarajuće izomere 2-etil-2-fenilglutarimida i monoamide 2-etil-2-fenilglutarne kiseline.

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