

New Compounds

5-Cyclohexylmethyl-5-arylhydantoins

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Received March 15, 1971

Certain 5-cycloalkylhydantoins possess anticonvulsant effects. The introduction of MeO groups in 5,5-disubstituted hydantoins has increased the drug efficacy.¹ We have prepared 5-cyclohexylmethyl-5-arylhydantoins, substituted with MeO groups in the aromatic ring; the new substances had no significant anticonvulsant activity.²

Experimental Section³

MeO Derivatives of α -Cyclohexylacetophenone.⁴— P_2O_5 (0.58 mole) and H_3PO_4 (d , 1.71, 1.0 mole) were heated at 120° with

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(1) A. Novelli and A. M. de Santis, *J. Med. Chem.*, **11**, 176 (1968).

(2) Pharmacological assays were performed by L. Pirro de Barán, Instituto Nacional de Farmacología y Bromatología. Mice were used for the experiments for anticonvulsant activity following the method described by J. W. Bastran, W. E. Krause, S. A. Ridlon, and N. Ercoli, *J. Pharmacol. Exp. Ther.*, **127**, 75 (1959).

(3) Melting points were taken on a Fischer-Johns apparatus and are uncor. Ir spectra were measured on a Perkin-Elmer Model 137 E infracord. Satisfactory ir spectra were recorded for all compds. Microanalyses were per-

continuous stirring for 4 hr. After cooling to 70–80°, 0.17 mole of cyclohexylacetic acid⁵ and 0.17 mole of the respective methoxybenzene were added. The mixt was heated with stirring at this temp for 5 hr, cooled, and poured slowly into cold H_2O with stirring. The solid was filtered, washed (H_2O , 10% NaOH, H_2O), and recrystd ($EtOH-H_2O$).

α -Cyclohexyl-4-methoxyacetophenone had mp 44–45° (lit.⁶ mp 43–44°), yield 85%. *Anal.* ($C_{15}H_{20}O_2$) C, H.

α -Cyclohexyl-3,4-dimethoxyacetophenone had mp 51–52°, yield 72%. *Anal.* ($C_{16}H_{22}O_3$) C, H.

5-Cyclohexylmethyl-5-phenylhydantoins.—A suspension contg 8.25 g of KCN and 20.5 g of $(NH_4)_2CO_3$ in 50 ml of H_2O was added to a soln of 5 g of the appropriate ketone in 100 ml of DMF. The mixt was heated at 80–90° for 2 hr and then at 90–100° for 8 hr. H_2O (100 ml) was added, and the mixt was filtered. The filtrate was acidified with AcOH, and the hydantoin was collected by filtration, washed (H_2O), and recrystd ($EtOH-H_2O$).

5-Cyclohexylmethyl-5-phenylhydantoin had mp 178–179°, yield 85%. *Anal.* ($C_{16}H_{20}N_2O_2$) C, N; H: calcd, 7.35; found, 8.05.

5-Cyclohexylmethyl-5-(4-methoxyphenyl)hydantoin had mp 229–230°, yield 82%. *Anal.* ($C_{17}H_{22}N_2O_3$) C, H, N.

5-Cyclohexylmethyl-5-(3,4-dimethoxyphenyl)hydantoin had mp 241–242°, yield 78%. *Anal.* ($C_{18}H_{24}N_2O_4$) C, H, N.

Acknowledgment.—This study was supported by a grant from the Consejo Nacional de Investigaciones Científicas y Técnicas de la República Argentina.

formed at this laboratory. Where anal. are indicated only by symbols of the elements, anal. results obtained for those elements were within $\pm 0.4\%$ of the theor values.

(4) α -Cyclohexylacetophenone was obtd as a colorless oil (92% yield) by the procedure of C. D. Nenitzescu, E. Cioranescu, and M. Maican, *Ber.*, **74B**, 687 (1941).

(5) R. Adams and J. R. Marshall, *J. Amer. Chem. Soc.*, **50**, 1970 (1928).

(6) P. Rugli and A. Businger, *Helv. Chim. Acta*, **24**, 1112 (1941).

Book Reviews

Advances in Drug Research. Volume 5. Edited by N. J. HARPER and ALMA B. SIMMONDS. Academic Press, New York, N. Y. 1970. vii + 278 pp. 23.4 × 16.6 cm. \$13.00

Facts are easier to review than therapeutic areas for which a mass of data has accumulated but no cogent interpretation has been presented. A survey of biologically active benzo[b]thiophene derivatives falls in the first category. These compounds, conceived serendipically or rationalized as isosteres of indole or naphthalene analogs, are described physicochemically and pharmacologically by an authority on aromatic sulfur-containing systems (E. Campaigne, with 3 students). Similarly, on a pharmacologically more searching level, R. T. Brittain, D. Jack, and A. C. Ritchie review β -adrenergic stimulants, drawing on many ideas of Larsen and of Bloom to support their mechanistic contentions.

The second type of approach is represented in reviews of endogenous bronchoactive substances and their antagonism (H. O. J. Collier) and the role of slow-reacting substance in asthma (W. E. Brocklehurst). Here biological explanations break down, and the authors have to pull out all stops to paint a convincing picture of asthma and antiasthmatic drugs. Never-

theless, the urgency and timeliness of the subject gives these chapters added significance.

J. S. G. Cox and his colleagues have studied disodium cromoglycate chemically, and for every conceivable biological activity in many species including man. This chapter may well be referred to as a prototype review the F.D.A. would like to get on every new drug. One is awed by the effort that has been expended on this one antiasthmatic compound.

A chapter by C. F. Chignell on spectroscopic techniques for the study of drug interactions with biological systems stands out because of its readability. The fundamentals of every known standard spectroscopy are explained in simple words, and after the reader feels at home in a given method, applications to drug-macromolecule interaction (mostly with soluble proteins and "silent receptors") are described. Since we depend on spectroscopic methods for qualitative and quantitative analysis and interpretation of all such drug interaction, this collection of pertinent examples will be particularly welcome to every kind of medicinal scientist.

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