ported to possess appreciable hypoglycemic activity. Based on these observations, several indanamides like 1-*N*-alkylacetamidoindans[4] and 3-oxo-1-*N*-alkylacetamidoindans have been synthesized to evaluate their hypoglycemic activity. None of these compounds, however, possessed any hypoglycemic activity.

Experimental Section[5]

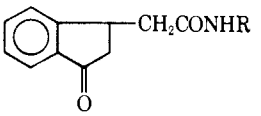
Methyl 3-Oxoindan-1-acetate.—3-Oxoindan-1-acetic acid[6] (27 g) was esterified with dry MeOH (90 ml) in the presence of dry HCl (6 g) by refluxing on a steam bath for 8 hr. The crude ester was crystd from EtOAc–petr ether (bp 40–60°) in 90% yield, mp 67–68°. *Anal.* ($C_{12}H_{12}O_3$) C, H.

3-Oxo-1-*N*-alkylacetamidoindan. A.—A mixt of methyl 3-oxoindan-1-acetate (1 mole) and the appropriate alkylamine (2 moles) was heated in a sealed tube on steam bath for 6 hr. The reaction mass was poured into H_2O, acidified with 2 *N* HCl, either filtered or extd (PhH), and washed (H_2O). The crude product was crystd from PhH–petr ether (bp 40–60°) as shining crystals.

b.—$SOCl_2$ (5 ml) was added dropwise to a mixt of 3-oxoindan-1-acetic acid[6] (3 g) and dry PhH (120 ml) with stirring till the evoln of HCl ceased. Approx 90 ml of PhH was distd off and the residual mass (3-oxoindan-1-acetyl chloride) was cooled in ice water. The cooled soln of 3-oxoindan-1-acetyl chloride (1 mole) was added dropwise under stirring to a soln of alkylamines (2.5 moles) in PhH (40 ml) with the simultaneous addn of 2 *N* NaOH to keep the mass alk. After stirring for 2 hr it was either filtered or extd (PhH), washed (H_2O), and purified by crystn from PhH–petr ether (bp 40–60°) as shining crystals (see Table I).

TABLE I

3-OXO-1-*N*-ALKYLACETAMIDOINDANS



R	Mp, °C	Empirical formula[c]
Me[a]	144–146	$C_{12}H_{13}O_2N$
Et[b]	120–121	$C_{13}H_{15}O_2N$
n-Pr[b]	116–118	$C_{14}H_{17}O_2N$
n-Bu[b]	97–98	$C_{15}H_{19}O_2N$

[a] Prepd from ester. [b] Prepd from acid chloride. [c] *Anal.* C, H, N.

Acknowledgment.—The authors' thanks are due to Bristol Laboratories, Syracuse, N. Y., for the hypoglycemic test report.

(4) A. U. De and B. Pathak, *J. Med. Chem.*, **13**, 152 (1970).

(5) Analytical results were within ±0.4% of the theoretical values. All melting points are uncorrected.

(6) R. H. Manske, *J. Amer. Chem. Soc.*, **53**, 1104 (1931).

Anti-*Trichinella spiralis* Activity of Some 1-Carbamoyl-3-methyl-2-pyrazolin-4,5-dione 4-Arylhydrazones

H. G. GARG

Department of Chemistry, University of Roorkee, Roorkee, India

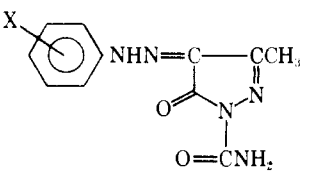
Received September 8, 1970

Heterocyclic compounds containing a carbamoyl group have been reported to possess various activities[1] due to their ability to inhibit acetylcholinesterase, probably by the transfer of a carbamoyl group to an active site of the enzyme. This report includes the potencies against *Trichinella spiralis* of several 1-carbamoyl-3-methyl-2-pyrazolin-4,5-dione 4-arylhydrazones which were described earlier in connection with our work on potential antidiabetics.[2]

The compounds were prepared as described previously[2,3] and were tested in mice and have shown the order of decreasing potency listed in Table I.

TABLE I

ANTI-*Trichinella* ACTIVITY[a]



No.	X	Mp, °C	Mean worm count: Control	Mean worm count: Drug	% reduction[a]
1	2-Cl-4-NO_2	210[b]	396	326	17.7
2	2,5-Cl_2	258–259[c]	396	388	2.0
3	2-Cl-6-Me	226[c]	396	394	0.5
4	4-NO_2	257–258[c]	495	536	0
5	2,6-Cl_2	200[c]	396	403	0

[a] Drug administration was po in Charles River Mice. Compound effectiveness was calcd as a percentage reduction based on the following formula. % reduction = 100 − [(Mean of medicated group worm count)/(mean of unmedicated control group worm count)]. [b] Ref 2. [c] Ref 3.

Acknowledgment.—The author is thankful to Dr. Maxwell Gordon (SK and F Laboratories, Philadelphia, Pa.) for making testing data available and to Professor W. U. Malik, Head of the Chemistry Department, for encouragement.

(2) H. G. Garg and S. N. Mehra, *J. Indian Chem. Soc.*, **38**, 325 (1961).

(3) H. G. Garg and P. P. Singh, *J. Chem. Soc. C*, 1141 (1969).

Modified Syntheses of 2,4,5-Trihydroxyphenylalanine, 2,4,5-Trihydroxyphenethylamine, and Analogs[1]

FRED G. H. LEE,* DONALD E. DICKSON,

Regis Chemical Company, Chicago, Illinois 60610

AND ALBERT A. MANIAN

Psychopharmacology Research Branch, National Institute of Mental Health, Chevy Chase, Maryland 20015

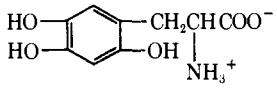
Received October 12, 1970

We are reporting new and more rewarding syntheses of 2,4,5-trihydroxyphenylalanine (I) (6-hydroxydopa),[2]

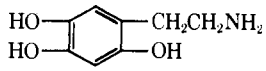
(1) This investigation was supported by the Psychopharmacology Research Branch, National Institute of Mental Health, Contract No. HSM-42-70-41.

(2) H. H. Ong, C. R. Creveling, and J. W. Daly, *J. Med. Chem.*, **12**, 458 (1969).

and 2,4,5-trihydroxyphenethylamine (II) (6-hydroxydopamine),[3] an important metabolite of 3,4-dihydroxyphenethylamine (dopamine).[4]



I



II

Experimental Section

Melting points were obtained on a Thomas-Hoover melting point apparatus and are uncorrected. Ir spectra were recorded on a Perkin-Elmer Infracord, Model 137. Microanalyses were performed by Micro-Tech Laboratories, Inc., Skokie, Ill.

2,4,5-Tribenzyloxybenzyl Chloride.—To a stirred soln of 2,4,5-tribenzyloxybenzyl alcohol[2] in 25 ml of $CHCl_3$ at 0° was added a soln of 12 ml of $SOCl_2$ in 25 ml of $CHCl_3$. The temp was maintained at −5° for 5 hr, the ice bath was removed, and the temp was allowed to rise to 18° for 1 hr. It was again lowered to −5° for 1 hr and solvents and excess reagents were removed below 50°. The oil was triturated with hexane which was decanted and discarded, the resulting solid was recrystd from hexane (Darco C-60), cooling only to room temp, to yield 2.0 g (45.1%), mp 82–83°. *Anal.* ($C_{28}H_{23}ClO_3$) C, H.

Benzyl β-(2,4,5-Tribenzyloxyphenyl)-α-nitropropionate.—To a cold soln of 0.7 g of Na in 20 ml of abs EtOH was added dropwise a sol of 6 g (0.035 mole) of benzyl nitroacetate[5] in 10 ml of abs EtOH. The resulting mixt was stirred in an ice bath for 30 min. After a soln of 12.4 g (0.028 mole) of 2,4,5-tribenzyloxybenzyl chloride in 25 ml of DMF was added, stirring was continued at room temp for 30 hr. After removal of solvent under vacuum, the residue was treated with hexane several times in order to remove the unreacted 2,4,5-tribenzyloxybenzyl chloride. The remaining solid was recrystd from abs EtOH several times to give 0.5 g (8.2%) of light yellow crystals, mp 100–102°. *Anal.* ($C_{39}H_{33}NO_7$) C, H, N.

2,4,5-Trihydroxyphenylalanine (I).—A mixt of 0.5 g (0.0008 mole) of benzyl β-(2,4,5-tribenzyloxyphenyl)-α-nitropropionate, 1 g of PtO_2, and 100 ml of EtOH was shaken in a Parr shaker at 3.5 kg/cm² of H_2 for 20 hr without isolation of amino ester intermediate. One gram of 10% Pd/C was added and the hydrogenation continued for another 20 hr. After flushing with SO_2, the mixt was filtered under N_2 and the solvent was removed under vacuum to give 200 mg of crude I. Recrystn from SO_2-satd H_2O–*i*-PrOH yielded 50 mg (20.2%) of white solid, mp 264–265° (lit.[6] mp 265°). *Anal.* ($C_7H_{11}NO_5$) C, H, N.

5-(2,4,5-Tribenzyloxybenzylidine)hydantoin.—A mixt of 82 g (0.192 mole) of 2,4,5-tribenzyloxybenzaldehyde,[7] 42 g (0.42 mole) of hydantoin, 42 g of NaOAc, 90 ml of AcOH, and 6 ml of Ac_2O was heated under reflux (140°) for 4.5 hr. Near the end of the reaction, some of AcOH was removed to allow the internal temp to rise to 160° for 10 min. The hot reaction mixt was poured into a large evap dish, and cooled with a stream of N_2. The hard mass was washed thoroughly with a large amt of cold H_2O, then with cold EtOH, and dried. The crude product was crystd from $CHCl_3$ to yield 48 g (49.5%) of yellow crystals, mp 190–192°. *Anal.* ($C_{31}H_{26}N_2O_5$) C, H, N.

5-(2,4,5-Tribenzyloxybenzyl)hydantoin.—A soln of 39 g (0.078 mole) of 5-(2,4,5-tribenzyloxybenzylidine)hydantoin in 500 ml of dioxane and 80 ml of H_2O was treated with 1.2 kg of 1% Na(Hg) at room temp with stirring. After 16 hr, the soln was decanted from Hg, dild with H_2O, filtered, and acidified with dil HCl. The crude product was collected by filtration, washed with H_2O, and dried. Cryst from C_6H_6 gave 31.0 g (79.5%) of product as white powder, mp 177–178.5°. *Anal.* ($C_{31}H_{28}N_2O_5$) C, H, N.

2,4,5-Tribenzyloxyphenylalanine.—A soln of 20 g (0.039 mole) of the corresponding benzylhydantoin in 380 ml of 2-methoxyethanol and 90 ml of H_2O containing 60 g of KOH was heated under reflux for 15 hr. The solvent was evapd *in vacuo* and the residue dissolved in 50% EtOH. Acidification with dil HCl gave 15 g (79.5%) of product. Crystn from MeOH gave white needles, mp 172–173°. *Anal.* ($C_{30}H_{27}NO_5$) C, H, N.

2,4,5-Trihydroxyphenylalanine (I).—A soln of 4.5 g (0.0092 mole) of the corresponding benzylated amino acid in 250 ml of abs MeOH was hydrogenated over 1.5 g of 5% Pd/C at 3.5 kg/cm² of H_2 at room temp for 20 hr. After flushing with SO_2, filtration, and evapn of the solvent *in vacuo*, the crude product was crystd from SO_2-satd H_2O–*i*-PrOH to give 0.7 g (35.7%) of colorless crystals, mp 264–265° (lit.[6] mp 265°). *Anal.* ($C_7H_{11}NO_5$) C, H, N.

2,4,5-Tribenzyloxy-β-nitrostyrene.—A mixt of 94 g (0.22 mole) of 2,4,5-tribenzyloxybenzaldehyde,[7] 8.5 g of NH_4OAc, and 1.05 l. of $MeNO_2$ was stirred at 120° for 5 hr. Cooling with an ice bath pptd a yellow solid which was collected and washed with H_2O, MeOH, and petr ether; yield 83.4 g, mp 138–140°. The filtrate was poured into 2.0 l. of H_2O and stirred for 30 min and the solid was collected. The combined solids were dried in a vacuum oven for 5 hr at 60° to give 85.4 g (81.4%) of yellow solid, mp 138–140°. *Anal.* ($C_{27}H_{25}NO_5$) C, H, N.

2,4,5-Tribenzyloxyphenethylamine·HCl.—A soln of 27.4 g (0.0586 mole) of 2,4,5-tribenzyloxy-β-nitrostyrene in 500 ml of dry THF was added dropwise with stirring under N_2 to a suspension of 27.4 g of LAH in 2.0 l. of dry THF. After the addition was complete (20 min), an additional 4.0 g of LAH was added. The reaction mixt was stirred and refluxed for 18 hr. With stirring and cooling in an ice bath, 100 ml of H_2O in 400 ml of THF was added dropwise and the resulting mixt was refluxed for 30 min. The grey solid was filtered and extd with 1.0 l. of hot THF. The combined THF solns were dried (Na_2SO_4) and evapd to an oil which solidified, mp 70–77°. This material was dissolved in abs EtOH and treated with 15 ml of satd Et_2O–HCl producing a solid, mp 160–163°. Recryst twice from abs EtOH gave 19.3 g (69.5%), mp 168–171°. *Anal.* ($C_{27}H_{29}NO_3$·HCl) C, H, N.

2,4,5-Trihydroxyphenethylamine·HCl (II).—A mixt of 15 g (0.0317 mole) of 2,4,5-tribenzyloxyphenethylamine·HCl, 250 ml of abs EtOH, and 5.0 g of 10% Pd/C was hydrogenated at room temp for 17 hr. It absorbed 0.11 mole of H_2 (theory: 0.095 mole) at 4.41 kg/cm². The mixt was filtered under N_2, and the solvent was removed under reduced pressure yielding 6.0 g (92%) of light grey solid, mp 230–232° dec. The crude product was treated with 35 ml of Et_2O–HCl (SO_2 gas was passed through briefly), and filtered. The solid was washed with Et_2O–HCl soln, then EtOH–Et_2O, and finally dried *in vacuo*, mp 231.5–233° dec. *Anal.* ($C_8H_{11}NO_3$·HCl) C, H, N.

***N*-Formyl-2,4,5-tribenzyloxyphenethylamine.**—To 21 ml of AcOCHO, cooled in an ice bath, was added slowly 23.9 g (0.054 mole) of 2,4,5-tribenzyloxyphenethylamine. The soln was stirred under N_2 at room temperature for 72 hr. After the excess anhydride was removed *in vacuo*, the residue was washed with H_2O, dil NH_4OH, NaCl soln, and dried. The crude product was recryst from petr ether–C_6H_6 to give 12.0 g (47.6%) of white cryst solid, mp 86–88° dec. *Anal.* ($C_{30}H_{29}NO_4$) C, H, N.

***N*-Methyl-2,4,5-tribenzyloxyphenethylamine·HCl.**—To a stirred soln of 10.0 g (0.0215 mole) of *N*-formyl-2,4,5-tribenzyloxyphenethylamine in 400 ml of distd THF was added 150 ml of 1.0 *M* diborane in THF over a period of 10 min. The resulting soln was stirred at room temperature for 16 hr, and decompd with 5% NaOH. The soln was extd (CH_2Cl_2) and dried (Na_2SO_4). After removal of solvent, the oily product was converted into the salt with satd EtOH–HCl. The crude HCl salt was recrystd from EtOH to give 8.0 g (65.5%) of white cryst solid, mp 161–163°. *Anal.* ($C_{30}H_{31}NO_3$·HCl) C, H, N.

The reaction conditions and work-up for the syntheses of the following compounds were identical with those just described.

N-Formyl-*N*-methyl-2,4,5-tribenzyloxyphenethylamine was obtained in 48.4% yield, mp 93–95°. *Anal.* ($C_{31}H_{31}NO_4$) C, H, N. *N,N*-Dimethyl-2,4,5-tribenzyloxyphenethylamine·HCl was obtained in 48.4%, mp 131–132°. *Anal.* ($C_{31}H_{33}NO_3$·HCl) C, H, N. *N,N*-Dimethyl-2,4,5-trihydroxyphenethylamine·HCl (30.7%), mp 167.5–169° dec. *Anal.* ($C_{10}H_{13}NO_3$·HCl) C, H, N.

2,4,5-Tribenzyloxy-β-methyl-β-nitrostyrene.—The reaction conditions and work-up for the reaction of 2,4,5-tribenzyloxybenzaldehyde with $EtNO_2$ were identical with those described for 2,4,5-tribenzyloxy-β-nitrostyrene. The yield was 88%. The yellow solid was recryst from C_6H_6–MeOH to give yellow needles, mp 125–127°. *Anal.* ($C_{30}H_{29}NO_5$) C, H, N.

α-Methyl-2,4,5-tribenzyloxyphenethylamine·HCl was obtained

(3) S. Senoh and B. Witkop, *J. Amer. Chem. Soc.*, **81**, 6222, 6231 (1959).
(4) (a) S. Senoh, C. R. Creveling, S. Udenfriend, and B. Witkop, *ibid.*, **81**, 1768 (1959). (b) S. Senoh, C. R. Creveling, S. Udenfriend, and B. Witkop, *ibid.*, **81**, 6236 (1959).
(5) A. Taylor, British Patent 835,521.
(6) Von A. Langeman and M. Scheer, *Helv. Chim. Acta*, **52**, 1095 (1969).
(7) B. Witkop, J. W. Daly, J. Benigni, R. Minnis, and Y. Kanaoka, *Biochemistry*, **4**, 2513 (1965).

analogously in 88.0% yield, mp 144–146°. A portion was crystd from EtOH–Et_2O to give colorless needles, mp 147–148°. *Anal.* ($C_{30}H_{31}NO_3 \cdot HCl$) C, H, N.

α-Methyl-2,4,5-tribenzyloxyphenethylamine Hydrogen Oxalate.—A portion of the base described above was converted into the salt in EtOH by addition of 1.0 equiv of oxalic acid at 45° for 10 min to yield 70.2% of salt, mp 173–175°, (EtOH–Et_2O). *Anal.* ($C_{30}H_{31}NO_3 \cdot C_2H_2O_4$) C, H, N.

Book Reviews

Fondamenti di Chimica Farmaceutica. Volume 2. By CARLO RUNTI. E. Lint, Trieste. 1970. 933 pp. 15 × 24 cm. Lire 14,000 (approx $22).

The first of this three-volume work has been reviewed [*J. Med. Chem.*, **13**, 788 (1970)]. The second volume consists of 6 chapters: Central Nervous System Depressants, Local Anesthetics, Neuromuscular Blockers, Central Nervous System Stimulants, Autonomic Nervous System Drugs, Antihistaminics and Antiserotonin Compounds. Antiinflammatory and antigout drugs follow a section on analgetic compounds included in the first chapter, and the beautifully organized section on β-adrenergic blockers is a part of the fifth.

As in the first volume, there is an abundance of tables and structures which add to the clarity of the book. There is a leading bibliography list, remarkably up-to-date, and a comprehensive index of generic and registered names.

Textbooks of this scope did not enjoy a very long shelf life in the rapidly innovating drug world of yesterday. In the present atmosphere of very cautious introduction of new drugs, it is likely that books such as this will maintain their usefulness and attractiveness for a long time to come. Its acquisition by libraries and professionals capable of reading it in the original Italian version is unreservedly recommended.

AYERST RESEARCH LABORATORIES R. DEGHENGHI
MONTREAL, CANADA