Table I. Results of Analysis for Erythrocyte Ghost Membrane[a]

Gas	Bunsen coeff in erythrocyte ghost[b]	Empirical solubility parameter, δ_1, for whole membrane	Empirical solubility parameter, δ_1, for membrane lipid alone
Neon	0.012	10.5	9.4
Hydrogen	0.024	10.6	9.6
Carbon monoxide	0.094	10.3	8.1
Nitrogen	0.096	9.5	7.3
Oxygen	0.113	10.1	8.3
Sulfur hexafluoride	0.151	10.5	9.9
	Mean ± S.D.	10.3 ± 0.40	8.7 ± 1.03

[a]The solubility data for CO_2 did not yield a value of δ_1 because solubility shows little dependence on the solvent solubility parameter. [b]See ref 10.

$cal^{1/2}$ $cm^{2/3}$. The empirical solubility parameters which we estimate from these data and our reference plots are given in Table I. They all fall within a range comparable to the experimental uncertainties with a mean δ_1 of 10.6 $cal^{1/2}$ $cm^{2/3}$. We conclude that regular solution theory may be applied in a self-consistent fashion to this membrane, and we may, therefore, predict Bunsen coefficients for ten additional gases for which we have reference plots using δ_1 = 10.6. These are He 0.01, Ar 0.11, Kr 0.32, Xe 1.5, CH_4 0.24, C_2H_6 1.7, C_2H_4 1.5, c-C_3H_6 5.3, CF_4 0.09, and N_2O 1.6.

Can this approach be generalized to other membranes? Measurements of the partition coefficients of benzyl alcohols[11] and spin labels[12] in lipid bilayer membranes of known compositions indicate that solvent power is a function of lipid composition and suggest that the empirical solubility parameter may vary systematically in some way with membrane composition. Characterization of δ_1 for a number of lipid bilayers might, therefore, allow the method to be applied *a priori* to any membrane of known composition, provided the heterogeneity of biomembranes can be successfully handled. That there is at least negligible specific binding to membrane protein in the red blood cell ghost by these gases is suggested by the consistency of our δ_1 estimates. This does not rule out nonspecific solvation in loosely packed hydrophobic membrane proteins. If we assume as a limiting condition membrane protein absorbs negligible solute, a lower limit to the solubility parameter of the lipid region may be fixed. In the present case, the erythrocyte ghost membrane is approximately 43 wt % lipid with roughly equal molar proportions of phospholipid and cholesterol.[13] Assuming that all the absorbed gas is concentrated in this lipid region allows one to place a mean lower limit on the empirical solubility parameter of the lipid region as 8.7 (Table I, last column). (The standard deviation of the estimate is slightly greater in this case reflecting the reduced slope of the log α *vs.* δ_1^2 plot often observed at lower δ_1.) Whether the value of 8.7 may be applied to the lipid portion of other membranes of similar compositions remains to be seen. If, however, regular solution theory can be applied to other membranes, then a wide range of applications will be available.[7] One might expect, however, that these would be limited to solute molecules small compared to the membranes dimensions.

Although not strictly comparable it is interesting to note some values of thermodynamic solubility parameters for simple solvents. Our minimum value of 8.7 for the lipid region compares to 7.3 for hexane and 8.0 for hexadecane. Hildebrand[7] has commented that the aliphatic hydrocarbons often behave as if their "practical" (*i.e.*, empirical in our terminology) solubility parameters are higher than those from heats of vaporization. The value of 10.3 for the whole membrane compares with 10.0 for carbon disulfide or 10.5 for bromoform and is higher than any values given for aliphatic hydrocarbons, suggesting that the membrane's structure may increase its cohesive energy density.

Finally, we note that the successful application of regular solution theory to a biological membrane is consistent with current notions of lipid bilayer membrane fluidity.

Conclusion

A semiempirical method, based on regular solution theory, has been proposed for predicting the solubility of gaseous solutes in membranes. Literature values for the solubility of six gases in the erythrocyte ghost membrane provide a test of the method and yield a self-consistent value of the membrane's solubility parameter. The analysis may be used to predict the solubility of other gases in this membrane.

Acknowledgments. This work was supported by the National Institute of General Medical Sciences (Contract No. GM 25904-06) and by the Office of Naval Research, Physiological Branch (Contract No. N00014-73-A-0340-0001) with funds provided by the Naval Bureau of Medicine and Surgery. L. J. B. is a Canadian Medical Research Council Fellow.

References

(1) S. J. Singer and G. L. Nicholoson, *Science*, **175**, 720 (1972).
(2) R. Fettiplace, S. M. Andrews, and D. A. Haydon, *J. Membrane Biol.*, **5**, 277 (1971).
(3) W. L. Hubbell and H. M. McConnell, *J. Amer. Chem. Soc.*, **93**, 314 (1971).
(4) K. W. Miller, W. D. M. Paton, R. A. Smith, and E. B. Smith, *Anesthesiology*, **36**, 339 (1972).
(5) R. Collander, *Acta Physiol. Scand.*, **13**, 363 (1947).
(6) J. M. Diamond and E. M. Wright, *Annu. Rev. Physiol.*, **31**, 581 (1969).
(7) J. H. Hildebrand, J. M. Prausnitz, and R. L. Scott, "Regular and Related Solutions," Van Nostrand-Reinhold, Princeton, N. J., 1970.
(8) G. Archer and J. H. Hildebrand, *J. Phys. Chem.*, **67**, 1830 (1963).
(9) E. Wilhelm and R. Battino, *Chem. Rev.*, **73**, 1 (1973).
(10) G. G. Power and H. Stegall, *J. Appl. Physiol.*, **29**, 145 (1970).
(11) C. M. Colley and J. C. Metcalfe, *FEBS Lett.*, **24**, 241 (1972).
(12) H. M. McConnell, L. Wright, and B. G. McFarland, *Biochem. Biophys. Res. Commun.*, **47**, 273 (1972).
(13) G. Guidotti, *Annu. Rev. Biochem.*, **41**, 731 (1972).

Annelated Thyroxine Analogs

Michael T. Cox,* W. Gary Bowness, and Jim J. Holohan

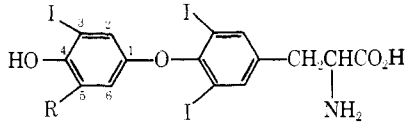
Imperial Chemical Industries Ltd., Pharmaceuticals Division, Alderley Park, Macclesfield, Cheshire, SK10 4TG, England. *Received April 22, 1974.*

The diverse activity of the thyroxine molecule (1) has encouraged much synthetic effort over the last few decades (for a recent review, see ref 1). Besides the various molecular modifications that have been carried out in order to try to improve or retain thyroxine-like activity, attempts have also been made to dissociate the various activities. The work of Blank and coworkers is noteworthy in that they achieved some separation of hypocholesterolemic, cardiac, and metabolic effects.[2]

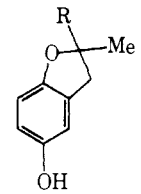
Although increased heart size, weight, and rate can be a result of hormone-induced hypermetabolism, there are indications that thyroid hormones exert a direct action on the myocardium.[3] We have sought to provide further examples of a separation of activities by studying the effects of thyroxine on body composition in relation to the cardiac hypertrophy and hyperphagia associated with thyroxine-induced increased metabolic rate.

It has been demonstrated that the replacement of iodine in the outer ring of triiodothyronine (2) by a small alkyl group, especially isopropyl, confers high thyromimetic activity on the resultant molecule.[4] It has also been shown that methylation of the phenolic hydroxyl group in 2 reduces toxicity and potency but increases selectivity of action.[2,5] We have attempted to combine these features by preparing compounds cyclized between positions 3 and 4 of the outer ring.

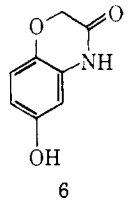
The first compounds prepared were derived from alkyl-substituted 5-hydroxy-2,3-dihydrobenzofurans (3).[6] The classical route from a protected 2,6-dinitro tyrosine derivative *via* the appropriate dinitro diphenyl ethers (4, R′ = H or CH_3) was used. After modified tetrazotization and iodination,[7] the protecting groups were removed (1:1 concentrated HCl–AcOH), without cleavage of the dihydrofuran ring, to afford the amino acids 5. These compounds possessed considerable thyromimetic properties but lacked selectivity of action. We sought to improve on this by giving the molecule different binding and/or transport characteristics; other bridging groups between positions 3 and 4 of the outer ring were utilized.



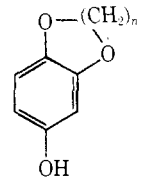
1, R = H
2, R = I



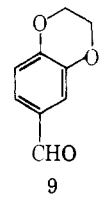
3, R = H or Me



6



7, n = 1
8, n = 2



9

Reaction sequences similar to those described above were carried out with the hydroxybenzoxazinone (6),[8] 3,4-methylenedioxyphenol (7),[9] and 1,4-benzodioxan-6-ol (8)[10],† giving the protected amino acids 10–12. (The methyl ester of the protected tyrosine was used in this work.) Of the three protected acids, only 12 could be converted to the corresponding free amino acid 13. Base hydrolysis of 10 gave the acid 14 but attempted acid or base hydrolysis of the dioxolo derivative 11 resulted in decomposition.

The compounds were examined for their ability to reduce the size of the parametrial fat organ of female mice over a 10-day administration period. Their effects on food intake and heart weight were also monitored.‡

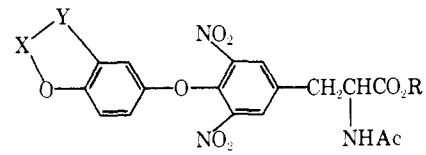
†Prepared by peracetic acid oxidation of 9[11] followed by hydrolysis (KOH-MeOH).

‡We thank Dr. S. E. Jaggers for providing the biological data.

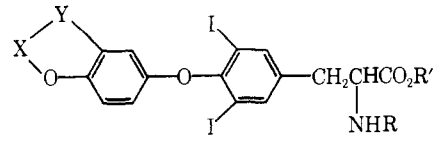
Table I. Thyromimetic Effect of Thyroxine Analogs

Compound	% in diet	% heart wt change	% change in fat organ	% change in food intake
L-Thyroxine	0.0004	+21	−33	+18
(1)	0.0002	+22	−25	+23
5, R″ = Me	0.04	+23	−25	+25
5, R″ = H	0.01	+24	−47	+16
	0.005	+22	−20	+16
11	0.01	+23	−7	+7
	0.005	+16	−12	+7
13	0.04	+12	−26	+10
14	0.04	+8	+2	−5

Screening test results are shown in Table I. Further examination revealed that the thyromimetic effect on heart weight and food intake was observed at lower dose levels than the effect on fat organs. Thus the compounds possessed no useful separation of activity.



4, X = -CCH_2R'-; Y = CH_2; R′ = H or Me; R = Et
15, X = CH_2; Y = CONH; R = Me
16, X = CH_2; Y = O; R = Me
17, X = CH_2; Y = CH_2O; R = Me



5, X = -CCH_3R''-; Y = CH_2; R″ = H or Me; R = R′ = H
10, X = CH_2; Y = CONH; R = Ac; R′ = Me
11, X = CH_2; Y = O; R = Ac; R′ = Me
12, X = CH_2; Y = CH_2O; R = Ac; R′ = Me
13, X = CH_2; Y = CH_2O; R = R′ = H
14, X = CH_2; Y = CONH; R = Ac; R′ = H
18, X = CH_2; Y = CH_2O; R = Ac; R′ = H

Experimental Section

Bioassay. Compounds were administered in the diet to groups of ten female mice over a 10-day period. The parametrial fat organs and hearts were dissected out and weighed and compared with the control group of 50 mice. The total food intake over the 10-day period was also measured.

Synthesis. Melting points were determined on a Büchi-Tottoli apparatus and are uncorrected. Where analyses are indicated only by symbols of the elements, analytical values obtained for those elements were within ±0.4% of the theoretical values.

***N*-Acetyl-3,5-dinitro-L-tyrosine Methyl Ester.** *N*-Acetyl-3,5-dinitro-L-tyrosine (50 g, 0.18 mol)[12] was dissolved in MeOH (250 ml) containing concentrated H_2SO_4 (1.25 ml) and stirred overnight. After dilution with water and neutralization, the solid was filtered and crystallized from water: yield 45 g; mp 118–120°. *Anal.* ($C_{12}H_{13}N_3O_8$) C, H, N.

***N*-Acetyl-4-(3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-6-yloxy)-3,5-dinitro-L-phenylalanine Methyl Ester (15).** The foregoing tyrosine methyl ester (9.7 g, 0.03 mol) and *p*-toluenesulfonyl chloride (5.7 g, 0.03 mol) were heated in pyridine (130 ml) at 100° for 10 min. To the dark red solution was added 6-hydroxy-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine (6, 9.9 g, 0.06 mol) and the mixture heated at 130° for 2 hr. The reaction mixture was cooled to room temperature and added to a mixture of ice (200 g), H_2O (650 ml), and concentrated HCl (65 ml). The mixture was stirred rapidly with $CHCl_3$ (325 ml) for 30 min[13] and then filtered to remove

some black material. The $CHCl_3$ layer was washed with 2 *N* HCl and H_2O before evaporating to a brown solid (9.9 g). Chromatography on silica gel using EtOAc as eluent afforded a solid: 7.2 g; mp 182–195°. Recrystallization from a small volume of EtOAc gave a yellow solid: yield 6.2 g; mp 198–201°. *Anal.* ($C_{20}H_{18}N_4O_{10}$) C, H, N.

The following compounds were prepared in a similar manner but were used without purification in further reactions: *N*-acetyl-4-(1,3-benzodioxol-5-yloxy)-3,5-dinitro-L-phenylalanine methyl ester (**16**); *N*-acetyl-4-(2,3-dihydro-1,4-benzodioxin-6-yloxy)-3,5-dinitro-L-phenylalanine methyl ester (**17**); *N*-acetyl-4-(2-methyl-2,3-dihydrobenzofuran-5-yloxy)-3,5-dinitro-L-phenylalanine ethyl ester (4, R′ = H); *N*-acetyl-4-(2,2-dimethyl-2,3-dihydrobenzofuran-5-yloxy)-3,5-dinitro-L-phenylalanine ethyl ester (4, R′ = Me).

***N*-Acetyl-4-(3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-6-yloxy)-3,5-diiodo-L-phenylalanine (14).** The dinitrobenzoxazine derivative **15** (5 g, 0.011 mol) was hydrogenated at atmospheric pressure in glacial AcOH (100 ml) in the presence of 10% Pd/C (1 g) until H_2 uptake had ceased (70 min). The solution was cooled in an ice bath and concentrated H_2SO_4 (20 ml) added, and the catalyst was removed by filtration. The diamine solution was placed in a pressure equalizing dropping funnel under N_2 and added during 1 hr to a stirred solution of $NaNO_2$ (3.4 g, 0.05 mol) in concentrated H_2SO_4 (37.5 ml, prepared at 50°) to which glacial AcOH (37.5 ml) had been added. The mixture was maintained at −5° during addition of the diamine; concentrated H_2SO_4 (37 ml) was added concomitantly to prevent freezing. When the addition was complete the orange-red solution was stirred at −5° for 1 hr and then added rapidly with vigorous stirring to a solution of I_2 (13.4 g), NaI (18.6 g), and urea (1.92 g) in H_2O (190 ml) and $CHCl_3$ (190 ml) at 0°. The resultant mixture was stirred 1 hr at <10°, 1 hr at room temperature, and 1 hr at 40° and then filtered. The $CHCl_3$ layer was separated, washed with H_2O, 10% $NaHSO_3$ solution, H_2O and brine, and dried (Na_2SO_4). Evaporation gave a solid foam which crystallized from EtOAc as a buff powder: yield 2.0 g; mp 225–227°.

The powder (1.0 g) was dissolved in dioxane (30 ml). To this stirred solution, a solution of KOH (0.88 g) in water (4 ml) was added. An oil formed and after 10 min the whole mixture was evaporated. H_2O was added to the residue and the solution adjusted to pH 5 (dilute HCl). The resultant solid was recrystallized from Me_2CO-H_2O as an off-white solid: yield 0.5 g; mp 210–212° dec. *Anal.* ($C_{19}H_{16}I_2N_2O_6$) C, H, N.

4-(1,4-Benzodioxan-6-yloxy)-3,5-diiodo-L-phenylalanine (13). The crude dinitrobenzodioxane derivative **17** (11.2 g) was hydrogenated, tetrazotized, and iodinated as described above and furnished *N*-acetyl-4-(1,4-benzodioxan-6-yloxy)-3,5-diiodo-L-phenylalanine methyl ester (**12**) as a solid foam, 8 g.

The ester **12** (2.5 g) was dissolved in EtOH (75 ml) and a solution of KOH (2.15 g) in H_2O (10 ml) added with stirring. After 10 min the solution was evaporated to dryness and the residue acidified to pH 5 (dilute HCl). The solid was filtered and recrystallized from Me_2CO-H_2O furnishing the acetamido acid **18** as an off-white solid: yield 1.3 g; mp 222–223° dec. *Anal.* ($C_{19}H_{17}I_2NO_6$) C, H, N.

The protected amino acid **12** (3 g) was dissolved in concentrated HCl-AcOH (60 ml of 1:1) and heated under reflux for 2 hr. The mixture was cooled and filtered and the solid recrystallized from MeOH-H_2O giving the title compound **13** as an off-white powder: yield 0.75 g; mp 258–260°. *Anal.* ($C_{17}H_{15}I_2NO_5$) C, H, N.

***N*-Acetyl-4-(2*H*-1,3-benzodioxol-5-yloxy)-3,5-diiodo-L-phenylalanine Methyl Ester (11).** The crude dinitrobenzodioxole **16** (7.8 g) was hydrogenated, tetrazotized, and iodinated as described for the foregoing compounds, furnishing the title compound as a pale brown solid: yield 6.9 g; mp 134–137°. Recrystallization from EtOH raised the melting point to 153–155°. *Anal.* ($C_{19}H_{17}I_2NO_6$) C, H, N.

4-(2,2-Dimethyl-2,3-dihydrobenzofur-5-yloxy)-3,5-diiodo-L-phenylalanine (5, R″ = Me). Hydrogenation, subsequent tetrazotization, and iodination of the crude dinitrodihydrobenzofuran derivative 4 (R′ = Me, 4 g) afforded the protected amino acid as a solid foam. This was hydrolyzed in 1:1 HCl-AcOH at reflux. Decolorization (charcoal-MeOH) and crystallization (MeOH-H_2O) afforded the somewhat light-sensitive product: yield 570 mg; mp 224–227°. *Anal.* ($C_{19}H_{19}I_2NO_4$) C, H, N.

4-(2-Methyl-2,3-dihydrobenzofur-5-yloxy)-3,5-diiodo-L-phenylalanine (5, R″ = H). The crude dinitrodihydrobenzofuran derivative 4 (R′ = H, 3.4 g) was hydrogenated, tetrazotized, iodinated, and hydrolyzed as described for the foregoing compound. The product (1 g) was recrystallized three times from MeOH-H_2O: mp 223–226°. *Anal.* ($C_{18}H_{17}I_2NO_4$) C, H, N.

References

(1) E. C. Jorgensen in "Medicinal Chemistry," 3rd ed, part II, A. Burger, Ed., Wiley-Interscience, New York, N. Y., 1970, p 838.
(2) B. Blank, C. M. Greenberg and J. F. Kerwin, *J. Med. Chem.*, **7**, 53 (1964).
(3) (a) G. Howitt and D. J. Rowlands, *Lancet*, 1, 628 (1966); (b) R. A. Buccino, J. F. Spann, Jr., P. E. Pool, E. H. Sonnenblick, and E. Braunwald, *J. Clin. Invest.*, **46**, 1669 (1967); (c) F. J. Kessler, H. J. Michels, and P. W. Waldorf, *Verh. Deut. Ges. Inn. Med.*, **76**, 455 (1970).
(4) (a) C. M. Greenberg, B. Blank, F. R. Pfeiffer, and J. F. Pauls, *Amer. J. Physiol.*, **205**, 821 (1963); (b) B. Blank, F. R. Pfeiffer, C. M. Greenberg, and J. F. Kerwin, *J. Med. Chem.*, **6**, 560 (1963); (c) S. B. Barker, M. Shimada, and M. Makiuchi, *Endocrinology*, **76**, 115 (1965); (d) M. Wool, V. S. Fang, and H. A. Selenkow, *ibid.*, **78**, 29 (1966); (e) R. E. Taylor, Jr., T. Tsuchih, S. B. Barker, and E. C. Jorgensen, *ibid.*, **80**, 1143 (1967).
(5) R. G. Herrmann, C. C. Lee, and R. Parker, *Arch. Int. Pharmacodyn. Ther.*, **133**, 284 (1961).
(6) J. A. Chenicek and W. K. T. Gleim to Universal Oil Products Co., U. S. Patent 2,599,810 (1952).
(7) E. C. Jorgensen and P. A. Lehman, *J. Org. Chem.*, **26**, 897 (1961).
(8) J. R. Geigy AG, Swiss Patent 308,193 (1955).
(9) J. Böeseken, W. D. Cohen, and C. J. Kip, *Recl. Trav. Chim. Pays-Bas*, **55**, 815 (1936).
(10) P. M. Heertjes, B. J. Knape, H. C. A. van Beek, and K. van den Boogaart, *J. Chem. Soc.*, 3445 (1957).
(11) M. Tomita and T. Takahashi, *Yakugaku Zasshi*, **77**, 448 (1957); *Chem. Abstr.*, **51**, 14728*b* (1957).
(12) J. R. Chalmers, G. T. Dickson, J. Elks, and B. A. Hems, *J. Chem. Soc.*, 3424 (1949).
(13) G. A. Neville and R. Y. Moir, *Can. J. Chem.*, **47**, 2787 (1969).

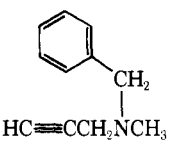
Potential Antifertility Agents. 5. 2,3-Diphenyl-1-(*N*-methyl-*N*-propargyl)aminoindenes[1]

R. R. Crenshaw,* Thomas A. Jenks, and Gabriel Bialy

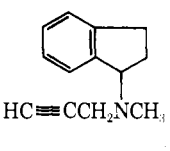
Research Division, Bristol Laboratories, Division of Bristol-Myers Company, Syracuse, New York 13201.

Received April 29, 1974

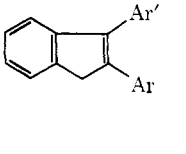
A number of inhibitors of the enzyme monoamine oxidase (MAO) are known to disrupt pregnancy at various stages in rodents.[2,3] It has been demonstrated that intrauterine instillation of the MAO inhibitor pargyline **1** in humans successfully produced interruption of pregnancy.[4]



1



2



3

An indan **2** structurally related to pargyline retains potent MAO inhibitory activity[5] but apparently has not been tested for antifertility activity. Substituted 2,3-diarylindene derivatives **3**[6] are potent antifertility agents in mammals owing to their estrogenicity and/or antiestrogenicity.[6,7] These observations suggested to us synthesis of the indenes **7c** and **7f** which incorporate structural features of **2** and **3**. It seemed possible that the diarylindene portion of **7c** or **7f** might serve as a carrier to deliver to the uterine environment a moiety analogous to that present in **1** which could produce a pregnancy-inhibiting action *via* MAO inhibition[2-4] or some other effect resultant from the molecular configuration.

Chemistry. Ketones **4**[8] and **5** were envisioned as starting materials for the preparation of **7c** and **7f**, respective-