Experimental Section

Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.3% of the theoretical values.

2,4-Diamino-6-chloro-5-pyrimidinecarboxaldehyde (IIb).—A suspension of 5.76 g (0.03 mole) of finely powdered 2-amino-4,6-dichloro-5-pyrimidinecarboxaldehyde[15] (IIa) in 250 ml of ethanolic NH_3 (prepared by saturating dry NH_3 in absolute EtOH at 5°) was stirred at room temperature for 18 hr. The resulting white precipitate was filtered off, washed (H_2O, cold EtOH), and dried at 80°. It was recrystallized from EtOH to give 4.3 g (83% yield) of analytically pure product which decomposed at 240° upon rapid heating: $\lambda_{max}^{pH\ 1}$ 264 mμ (ε 10,800), 305 (16,500); $\lambda_{max}^{pH\ 10}$ 264 mμ (ε 11,000), 303 (18,500). *Anal.* ($C_5H_5ClN_4O$) C, H, N.

2,4-Diamino-5-[N-(*p*-bromophenyl)formimidoyl]-6-(*p*-bromoanilino)pyrimidine (III, Y = Br, Z = H).—A mixture of 8.6 g (0.05 mole) of IIb and 25.8 g (0.15 mole) of *p*-bromoaniline was refluxed in 250 ml of EtOH containing 1 ml of concentrated HCl. A yellow solid gradually precipitated from the refluxing solution. After 3 hr the solid was filtered off from the boiling reaction mixture, triturated with Na_2CO_3 solution, filtered, washed well with H_2O, and finally recrystallized from a large volume of EtOH (1 g/1000 ml) to yield 13.6 g (59%); mp 269–272° dec; $\lambda_{max}^{pH\ 1}$ 269 mμ (ε 32,300) and 364 (12,900); $\lambda_{max}^{pH\ 10}$ 234 mμ (ε 18,000), 278 (24,000), and 362 (18,300). *Anal.* ($C_{15}H_{11}Br_2N_5$) C, H, N.

The following compounds have also been similarly prepared: their uv absorption bands were as expected. 2,4-Diamino-5-[N-(*p*-tolyl)formimidoyl]-6-(*p*-toluidino)pyrimidine (III, Y = CH_3; Z = H), 73% yield, mp 130–135° dec. *Anal.* ($C_{19}H_{20}N_6 \cdot HCl \cdot H_2O$) C, H, N. 2,4-Diamino-5-[N-(*p*-iodophenyl)formimidoyl]-6-(*p*-iodoanilino)pyrimidine (III, Y = I; Z = H), 66% yield, mp 257–258° dec. *Anal.* ($C_{15}H_{14}I_2N_6$) C, H, N. 2,4-Diamino-5-[N-(3,4-dichlorophenyl)formimidoyl]-6-(3,4-dichloroanilino)pyrimidine (III, Y, Z = Cl), 86% yield, mp 304–306° dec. *Anal.* ($C_{17}H_{12}Cl_4N_6 \cdot HCl$) C, H, N.

2,4-Diamino-6-(*p*-bromoanilino)-5-pyrimidinecarboxaldehyde (IV, Y = Br; Z = H).—A suspension of 5 g of III (Y = Br; Z = H) in 1000 ml of 0.1 *N* HCl was refluxed for 3 hr. The resulting solution, which still contained a small amount of insoluble material, was treated with decolorizing charcoal and filtered. The pH of the filtrate was brought to 8–9 by the careful addition of $NaHCO_3$, and the precipitated product was collected by filtration. It was washed (cold H_2O) and recrystallized from EtOH–H_2O to give 2.04 g (61% yield) of analytically pure product: mp 210–215°; $\lambda_{max}^{pH\ 1}$ 268 mμ (ε 38,800); $\lambda_{max}^{pH\ 0}$ 265 mμ (ε 30,500), 296 (17,200). *Anal.* ($C_{11}H_{10}BrN_5O$) C, H, N.

The following 5-pyrimidinecarboxaldehydes have also been similarly prepared. Their uv absorption bands were as expected. 2,4-Diamino-6-(*p*-toluidino)-5-pyrimidinecarboxaldehyde (IV, Y = CH_3; Z = H), 46% yield, mp 221–224°. *Anal.* ($C_{12}H_{13}N_5O$) C, H, N. 2,4-Diamino-6-(3,4-xylidino)-5-pyrimidinecarboxaldehyde (IV, Y, Z = CH_3) was obtained directly from IIb and 3,4-xylidine in 32% yield, mp 215–218°. *Anal.* ($C_{13}H_{15}N_5O$) C, H, N. 2,4-Diamino-6-(*p*-iodoanilino)-5-pyrimidinecarboxaldehyde (IV, Y = I; Z = H), 41% yield, mp 228–230°. *Anal.* ($C_{10}H_{10}IN_5O$) C, H, N.

Acknowledgment.—The authors wish to thank Mr. Leland R. Lewis, Mrs. Margaret L. Rounds, and Mr. John R. Gravatt for their valuable assistance in performing analytical and instrumental measurements.

Substituted 7,8,9,10-Tetrahydro-6H-cyclohepta[*b*]quinolines

CHEUK-MAN LEE

Organic Chemistry Department, Research Division, Abbott Laboratories, North Chicago, Illinois 60064

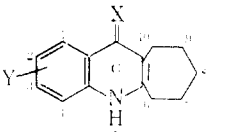
Received October 9, 1967

Recently a number of 4-N-substituted amino- and carbamoyl-2,3-polymethylenequinolines were synthesized and found to exhibit a wide spectrum of pharmacological properties.[1] An earlier report described the analeptic activity of aminocycloheptaquinoline.[2] In the present communication the synthesis of 11-substituted 7,8,9,10-tetrahydro-6H-cyclohepta[*b*]quinolines and the evaluation of these compounds for antidepressant activity is described.

7,8,9,10-Tetrahydro-6H-cyclohepta[*b*]quinolin-11-ones (Ia–i) (Table I) were prepared by refluxing

TABLE I

7,8,9,10-TETRAHYDRO-6H-CYCLOHEPTA[*b*]QUINOLIN-11-ONES AND -11-THIONES



Compd	X	Y	Mp, °C	Yield, %	Recrystn solvent[a]	Formula[b]
Ia[c]	O	H	330 dec	82[d]	A	$C_{14}H_{13}NO$
Ib[e]	O	2-Cl	381 dec	78	A	$C_{14}H_{12}ClNO$
Ic[e]	O	3-Cl	390 dec	60	A	$C_{14}H_{12}ClNO$
Id[e]	O	4-Cl	271 dec	50	A	$C_{14}H_{12}ClNO$
Ie	O	3-OCH_3	314 dec	28	A	$C_{15}H_{15}NO_2$
If	O	3-NO_2	355 dec	90[d]	B	$C_{14}H_{12}N_2O_3$
Ig	O	3-CF_3	355 dec	89	A	$C_{15}H_{12}F_3NO$
IIa	O	2,4-Cl_2	281–283	15	A	$C_{14}H_{11}Cl_2NO$
Ii	O	2,3,4-$(OCH_3)_3$	253 dec	17	A	$C_{17}H_{19}NO_4$
IIa	S	H	218–220	59	C	$C_{14}H_{13}NS$
IIb	S	2-Cl	250–252	60	C	$C_{14}H_{12}ClNS$
IIc	S	3-Cl	258–260	80	C	$C_{14}H_{12}ClNS$

[a] Reference 3. [b] These compounds are described by M. V. Sigal, Jr., B. J. Brent, and P. Marchini, U. S. Patent 3,232,945 (1966); *Chem. Abstr.*, **64**, 14174 (1966), by condensing *p*-chloro-, *m*-chloro-, and *o*-chloroaniline with 2-carbethoxycycloheptanone with melting points of 360, 360, and 264–265°, respectively. [c] Crude yield. [d] A = ethanol, B = DMF, and C = pyridine–water. [e] All compounds were analyzed for C, H, N. Where analyses are indicated only by symbols of the elements analytical results obtained for those elements were within ±0.3% of the theoretical values.

o-aminobenzoic acid and substituted *o*-aminobenzoic acids with cycloheptanone in xylene while removing water azeotropically. Using this procedure the yields were much higher than those obtained on heating the two reactants without solvent[3] and, in many cases, the crude products could be used for subsequent reactions without further purification. 7,8,9,10-Tetrahydro-6H-cyclohepta[*b*]quinoline-11-thiones (IIa–c) (Table I) were obtained by reaction of 7,8,9,10-tetrahydro-6H-cyclohepta[*b*]quinolin-11-ones (Ia–c) with phosphorus pentasulfide in pyridine (Scheme I). Alkylation of 7,8,9,10-tetrahydro-6H-cyclohepta[*b*]quinolin-11-ones (Ia–i) with dialkylaminoalkyl halides in dimethylformamide and sodium hydride yielded 11-dialkylaminoalkoxy-7,8,9,10-tetrahydro-6H-cyclohepta[*b*]-quinolines (IIIa–o) (Table II). Similar treatment of IIa–c with dialkylaminoalkyl halides gave 11-dialkylaminoalkylthio derivatives (IVa–g). 7,8,9,10-Tetrahydro-6H-cyclohepta[*b*]quinolin-11-ones (Ia–c) were converted to 11-chloro-7,8,9,10-tetrahydro-6H-cyclohepta[*b*]quinolines (Va–c) with phosphorus oxychloride.[4] Compounds Va–c were condensed with dialkyl-

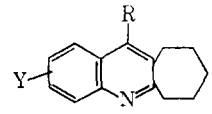
(1) G. K. Patnaik, M. M. Vohra, J. S. Bindra, C. P. Garg, and N. Anand, *J. Med. Chem.*, **9**, 483 (1966).

(2) N. Plotnikoff, J. Keith, M. Heimann, W. Keith, and C. Pepys, *Arch. Intern. Pharmacodyn.*, **146**, 406 (1963).

(3) W. H. Perkin, Jr., and S. G. P. Plant, *J. Chem. Soc.*, **131**, 2583 (1928).

TABLE II

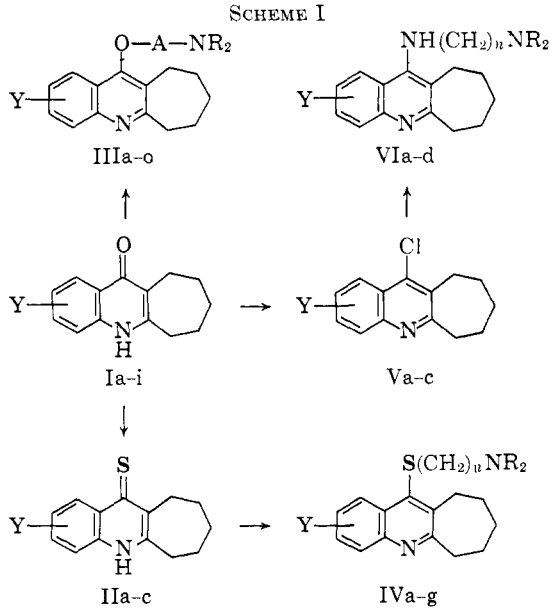
SUBSTITUTED 7,8,9,10-TETRAHYDRO-6H-CYCLOHEPTA[*b*]QUINOLINES



Compd	Y	R	Mp, °C	Yield, %	Recrystn[b] solvent	Formula[c]
IIIa	H	$OCH_2CH_2N(C_2H_5)_2$	270 dec	60	A	$C_{20}H_{28}N_2O\cdot 2HCl$
IIIb	H	$OC(CH_3)HCH_2N(CH_3)_2$	190 dec	66	D	$C_{19}H_{26}N_2O\cdot 2HCl$
IIIc	H	$O(CH_2)_3N(CH_3)_2$	245 dec	62	D	$C_{19}H_{26}N_2O\cdot 2HCl$[d]
IIId	2-Cl	$OCH_2CH_2N(CH_3)_2$	290 dec	77	D	$C_{18}H_{23}ClN_2O\cdot 2HCl$[e]
IIIe	2-Cl	$OC(CH_3)HCH_2N(CH_3)_2$	220 dec	80	D	$C_{19}H_{25}ClN_2O\cdot 2HCl$
IIIf	2-Cl	$O(CH_2)_3N(CH_3)_2$	260 dec	63	D	$C_{19}H_{25}ClN_2O\cdot 2HCl$[f]
IIIg	2-Cl	$OCH_2C(CH_3)HCH_2N(CH_3)_2$	248 dec	54	A	$C_{20}H_{27}ClN_2O\cdot 2HCl$
IIIh	3-Cl	$OC(CH_3)HCH_2N(CH_3)_2$	230 dec	78	D	$C_{19}H_{25}ClN_2O\cdot 2HCl$
IIIi	3-Cl	$O(CH_2)_3N(CH_3)_2$	320 dec	73	D	$C_{19}H_{25}ClN_2O\cdot 2HCl$
IIIj	4-Cl	$O(CH_2)_3N(CH_3)_2$	238 dec	50	D	$C_{19}H_{25}ClN_2O\cdot 2HCl$
IIIk	3-OCH_3	$OCH_2CH_2N(C_2H_5)_2$	152–153	81	D	$C_{21}H_{30}N_2O_2\cdot 2HCl$
IIIl	3-NO_2	$O(CH_2)_3N(CH_3)_2$	53–55	61	E	$C_{19}H_{25}N_3O_3$
IIIm	3-CF_3	$O(CH_2)_3N(CH_3)_2$	245 dec	52	D	$C_{20}H_{25}F_3N_2O\cdot 2HCl$
IIIn	2,4-Cl_2	$O(CH_2)_3N(CH_3)_2$	85–86	50	A	$C_{19}H_{24}Cl_2N_2O$[g]
IIIo	2,3,4-$(OCH_3)_3$	$O(CH_2)_3N(CH_3)_2$	205 dec	73	D	$C_{22}H_{32}N_2O_4\cdot 2HCl$
IVa	H	$SCH_2CH_2N(CH_3)_2$	69–70	64	E	$C_{18}H_{24}N_2S$
IVb	H	$SCH_2CH_2N(C_2H_5)_2$	191–193	62	D	$C_{20}H_{28}N_2S\cdot 2HCl$
IVc	H	$S(CH_2)_3N(CH_3)_2$	200 dec	72	D	$C_{19}H_{26}N_2S\cdot 2HCl$
IVd	2-Cl	$SCH_2CH_2N(CH_3)_2$	65–66	69	E	$C_{18}H_{23}ClN_2S$
IVe	2-Cl	$SCH_2CH_2N(C_2H_5)_2$	188–190	58	D	$C_{20}H_{27}ClN_2S\cdot 2HCl$
IVf	2-Cl	$S(CH_2)_3N(CH_3)_2$	198–200	65	D	$C_{19}H_{25}ClN_2S\cdot 2HCl$
IVg	3-Cl	$SCH_2CH_2N(C_2H_5)_2$	177–180	73	D	$C_{20}H_{27}ClN_2S\cdot 2HCl$
Va[a]	H	Cl	93–94	80	F	$C_{14}H_{14}ClN$
Vb	2-Cl	Cl	103–104	85	F	$C_{14}H_{13}Cl_2N$
Vc	3-Cl	Cl	86–87	74	F	$C_{14}H_{13}Cl_2N$
VIa	H	$NHCH_2CH_2N(CH_3)_2$	190–192	35	D	$C_{18}H_{25}N_3\cdot 2HCl$
VIb	H	$NH(CH_2)_3N(CH_3)_2$	213–215	42	D	$C_{19}H_{27}N_3\cdot 2HCl$
VIc	2-Cl	$NH(CH_2)_3N(CH_3)_2$	224–226	50	A	$C_{19}H_{26}ClN_3\cdot 2HCl$
VId	3-Cl	$NH(CH_2)_3N(CH_3)_2$	248–250	44	D	$C_{19}H_{26}ClN_3\cdot 2HCl$

[a] Reference 1. [b] A = ethanol, D = ethanol–ether, E = Skellysolve B, and F = acetone. [c] All compounds were analyzed for C, H, N. Where analyses are indicated only by symbols of the elements analytical results obtained for those elements were within ±0.4% of the theoretical values. [d] C: calcd, 61.56; found, 61.01. [e] C: calcd, 55.18; found, 54.80. [f] C: calcd, 56.23; found, 56.65. [g] N: calcd, 7.64; found, 8.14.

SCHEME I



aminoalkylamines in the presence of copper–bronze in sealed tubes at 180° for 24 hr to yield 11-dialkylaminoalkylamino derivatives (VIa–d).[4]

(4) L. J. Sargent and L. Small, *J. Org. Chem.*, **11**, 359 (1946).

Pharmacology.—Most of the compounds showed central stimulation. They were evaluated for antidepressant activity by the dopa response potentiation test[5] and were compared with imipramine and amitryptyline (Table III). Generally, the 11-dialkylaminoalkoxy derivatives (III) were more active than the 11-dialkylaminoalkylthio derivatives (IV). The 11-dialkylaminoalkylamino compounds (VI) had about the same activity as the 11-dialkylaminoalkoxy compounds (III) but they were more toxic.

Experimental Section[6]

7,8,9,10-Tetrahydro-6H-cyclohepta[*b*]quinolin-11-one (Ia).[3]—A mixture of 17.5 g (0.13 mole) of *o*-aminobenzoic acid, 19.0 g (0.17 mole) of cycloheptanone, and 200 ml of xylene was stirred and heated under reflux for 24 hr in a flask equipped with a Dean–Stark trap. The product was collected by filtering the hot mixture. An analytical sample was prepared by recrystallizing the product from an appropriate solvent.

Compounds Ib–i were prepared in the same manner except that the heating was continued for 48 hr or until no more water separated.

(5) (a) G. M. Everett, F. Will, and A. Evans, *Fed. Proc.*, **23**, 198 (1964); (b) G. M. Everett in Proceedings of the 1st International Symposium on Anti-depressant Drugs, Milan, 1966, S. Garattini and M. N. G. Dukes, Ed., Excerpta Medica Foundation, 1966, pp 164–167.

(6) Melting points were determined in an open capillary tube in a metal heating block and are uncorrected.

TABLE III

PHARMACOLOGICAL SCREENING RESULTS

Compd	Approx LD_{50}, mg/kg[a] ip	Approx LD_{50}, mg/kg[a] Oral	Antidepressant act.[b] Dopa response potentiation test ip	Antidepressant act.[b] Dopa response potentiation test Oral
Ia	800	900	++	++
Ib	2000	>2000	+	+++
Id	2000	>2000	+	+
Ig	750	>1000	++	++
Ii	>2000	>2000	+	++
IIa	800	>1000	+	+
IIb	800	>1000	++	+
IIIa	150	850	+	+
IIIb	60	500	+	+
IIIc	125	750	+	++
IIId	125	750	+	++
IIIe	100	400	++	++
IIIf	150	750	++	++
IIIg	100	400	+++	++
IIIh	100	750	+	+
IIIi	150	850	+	+++
IIIj	500	1500	+	+
IIIk	125	750	+	+
IIIl	125	400	+++	++
IIIm	500	1000	+	++
IIIn	500	1000	+	++
IIIo	100	400	++	++
IVa	400	600	+	+
IVb	125	600	+	+
IVc	125	600	+	+
IVd	500	>1000	+	+
IVe	125	600	++	++
IVf	90	600	++	+
IVg	300	1000	+	++
VIa	60	500	++	+
VIb	40	200	+	+
VIc	60	400	+	++
VId	15	75		+++
Imipramine	150	400	+++	+++
Amitryptyline	80	350	+++	+++

[a] The dihydrochlorides were administered as 5% solutions in water and other insoluble compounds as 2% suspensions in 0.3% tragacanth to albino Swiss–Webster mice. [b] Reference 5. Dose, 25 mg/kg; activity at 4 hr.

7,8,9,10-Tetrahydro-6H-cyclohepta[*b*]quinoline-11-thione (IIa).—P_2S_5, 44.4 g (0.2 mole), was added to a stirred suspension of 42.6 g (0.2 mole) of 7,8,9,10-tetrahydro-6H-cyclohepta[*b*]-quinolin-11-one in 400 ml of pyridine. The mixture was refluxed for 3 hr and poured gradually into 1600 ml of hot water. After cooling to room temperature, the product was filtered and recrystallized.

Compounds IIb and IIc were prepared as above.

11-[3-(Dimethylamino)propoxy]-7,8,9,10-tetrahydro-6H-cyclohepta[*b*]quinoline (IIIc).—A mixture of 8.5 g (0.04 mole) of 7,8,9,10-tetrahydro-6H-cyclohepta[*b*]quinolin-11-one, 2.2 g (0.048 mole) of NaH (53.2% suspension in oil), and 250 ml of DMF was stirred and heated in an oil bath, maintained at 75–80° for 2 hr under N_2. 3-(Dimethylamino)propyl chloride (9.7 g, 0.08 mole) was added, dropwise, and the mixture was heated at 75–80° for an additional 3 hr. After cooling, the mixture was filtered and the filtrate was evaporated *in vacuo*. The residue was diluted with H_2O and was extracted with ether. The extract was washed (H_2O), dried, and evaporated. The dihydrochloride was prepared by adding 2 equiv of HCl in *i*-PrOH to the residue (from ether extract) in EtOH, precipitated with ether, and refrigerated. All other compounds (III) were prepared as above except that IIIl and IIIn were isolated as bases.

11-[2-(Dimethylamino)ethylthio]-7,8,9,10-tetrahydro-6H-cyclohepta[*b*]quinoline (IVa).—A mixture of 5.7 g (0.025 mole) of 7,8,9,10-tetrahydro-6H-cyclohepta[*b*]quinoline-11-thione, 1.38 g (0.03 mole) of NaH (52% suspension in oil), and 80 ml of DMF was heated, with stirring, at 70–75° for 3 hr, under N_2. The solution was allowed to cool and 4.0 g (0.0375 mole) of 2-dimethylamino)ethyl chloride was added, dropwise. After the addition, the mixture was kept at 70–75° for 4 hr. On cooling, the mixture was filtered and the filtrate was evaporated *in vacuo*. The residue was diluted with water and extracted with ether. The extract was washed (H_2O) and dried (Na_2SO_4). After removal of the solvent, the residue solidified and was recrystallized.

Compound IVd was prepared in the same manner; IVb c and IVe–g were isolated as dihydrochlorides.

2,11-Dichloro-7,8,9,10-tetrahydro-6H-cyclohepta[*b*]quinoline (Vb).—2-Chloro-7,8,9,10-tetrahydro-6H-cyclohepta[*b*]quinolin-11-one (58 g, 0.234 mole) was added under stirring to 80 ml of freshly distilled $POCl_3$, cooled in an ice bath. The mixture was allowed to warm up to room temperature and then refluxed for 1 hr. After cooling, the mixture was poured over 1 kg of crushed ice and stirred for a few minutes. After 1 hr at room temperature, $CHCl_3$ (250 ml) was added and the solution was basified with NH_4OH. The aqueous layer was separated and extracted twice ($CHCl_3$). The combined extract was washed (H_2O), dried, and evaporated *in vacuo*. The residue was recrystallized.

Compounds Va and Vc were obtained in the same manner.

11-[2-(Dimethylamino)ethylamino]-7,8,9,10-tetrahydro-6H-cyclohepta[*b*]quinoline (VIa).—A mixture of 11.5 g (0.05 mole) of 11-chloro-7,8,9,10-tetrahydro-6H-cyclohepta[*b*]quinoline,[c] 8.8 g (0.1 mole) of 2-(dimethylamino)ethylamine, 0.5 g of copper-bronze powder, and a few crystals of I_2 was heated in a closed steel cylinder at 180° for 24 hr, then treated with H_2O and ether. The aqueous layer was separated and extracted with ether. The combined ether solution was washed (H_2O) several times, dried, and evaporated *in vacuo*. The product was isolated as the dihydrochloride as in previous examples.

Compounds VIb–d were prepared in the same way.

Acknowledgments.—The author is grateful to Dr. N. Plotnikoff and his staff for the pharmacological test results and to Messrs. O. Kolsto and V. Rauschel and their staff for elemental analyses.

Hypocholesteremic Agents. IV. Some Substituted Piperazines

H. B. WRIGHT AND D. L. MARTIN

Research Division, Abbott Laboratories, North Chicago, Illinois 60064

Received November 13, 1967

In a pharmacological study of chlorocyclizine[1a] and N-(β-phenyl-β-3-chlorophenyl-β-hydroxyethyl)-N′-methylpiperazine (**25**)[1b] Schmidt and Martin[2] found these compounds to be effective in causing a reduction in blood cholesterol concentration in mice although there was an increase in the cellular mass of the liver. This observation prompted us to prepare related compounds in the hope of finding one that would not show this adverse effect in the liver. This hope, however, was not realized. We prepared and tested 24 compounds related to the two piperazines mentioned above. These compounds showed varying degrees of lowering of blood cholesterol but this phenomenon was accompanied in general by an increased cellular mass in the liver. Many of the compounds had only weak activity and required the use of a high dosage. [*p*-

(1) (a) Diparalene®. (b) Prepared in this laboratory by R. J. Michaels and A. W. Weston.

(2) J. L. Schmidt and D. L. Martin, *Toxicol. Appl. Pharmacol.*, **7**, 257 (1965).