oil, 4.5 g (22 mmol) of trimethyloxosulfonium iodide, and 25 mL of Me_2SO was added a solution of 1.5 g (4.4 mmol) of the trienone **5c** in 40 mL of Me_2SO. The reaction mixture was stirred at room temperature in an atmosphere of nitrogen for 63 h. Then it was diluted with a large volume of water. The mixture was made slightly acidic with the addition of glacial HOAc. The solid was collected, washed with H_2O, and dried. It was chromatographed on silica gel. Elution with 20% EtOAc in C_6H_6 gave 0.62 g of a product, which was crystallized from EtOAc–hexane to furnish 0.15 (mp 208–211 °C), 0.27 (mp 204–211 °C), and 0.05 g of **7a** (mp 201–211 °C). The sample melting at 208–211 °C was submitted for analysis: UV λ_{max} (MeOH) 259–260 nm (ϵ 14 100); NMR τ 4.13 (s, C-4 H), 8.86 (s, C-19 H's), 9.01 (s, C-18 H's). Anal. ($C_{24}H_{30}O_3$) C, H.

3-(17β-Hydroxy-6α,7α-methylene-3-oxo-1,4-androstadien-17α-yl)propionic Acid γ-Lactone (6b). A 5.0 g (14.1 mmol) sample of **3b** was dehydrogenated with 5.0 g (22 mmol) of dichlorodicyanobenzoquinone in 250 mL of dioxane as described for the preparation of **6a**. The crude product was chromatographed on silica gel. Elution with 15% EtOAc–toluene gave fractions which were combined and crystallized from CH_2Cl_2–ether to afford 2.6 g (52%) of **6b**: mp 133–135 °C; UV λ_{max} (MeOH) 242–244 nm (ϵ 12 970); λ sh 267–270 nm (7401); IR ($CHCl_3$) 1770, 1660, 1618, 1600 cm^{-1}; NMR τ 3.07 (d, C-1 H, $J_{1,2}$ = 10 Hz), 3.75 [d (?), C-4 H, $J_{2,4}$ = 1.5 Hz (?)], 368 (dd, C-2 H, $J_{1,2}$ = 10 Hz, $J_{2,4}$ = 1.5 Hz), 6.53 (q, CH_3CH_2O, J = 7 Hz), 8.73 (s, C-19 H's), 8.80 [t (?), CH_3CH_2O, J = 7 Hz (?)], 8.95 (s, C-18 H's). Anal. ($C_{23}H_{28}O_3 \cdot 0.25C_4H_{10}O$) C, H.

3-[1α,2α,6α,7α-Bis(methylene)-17β-hydroxy-3-oxo-4-androsten-17α-yl]propionic Acid γ-Lactone (7b). Methylenation of 1.0 g (2.8 mmol) of **6b** with 100 mL of 0.47 N dimethyloxosulfonium methylide in Me_2SO was carried out as described for the preparation of the 6β,7β isomer **7a** from **6a**. The product, which did not need to be chromatographed, was crystallized from CH_2Cl_2–hexane to afford 0.69 g (66%) of **7b**: mp 251–253 °C; $[\alpha]^{25}_D$ +235.6° (c, 1.01, $CHCl_3$); NMR τ 4.27 (m, C-4 H), 8.75 (s, C-19 H's), 8.97 (s, C-18 H's); UV λ_{max} (MeOH) 257–258 nm (ϵ 11 654); IR ($CHCl_3$) 1765, 1645, 1614 cm^{-1}. Anal. ($C_{24}H_{30}O_3$) C, H.

Acknowledgment. We acknowledge our indebtedness to W. F. Pautsch, Dr. F. Radzialowski, D. Strandberg, Ms. E. T. Muir, and their associates for the biological results. We are grateful to E. J. Zielinski, A. J. Damascus, and their colleagues for the microanalytical and spectral determinations.

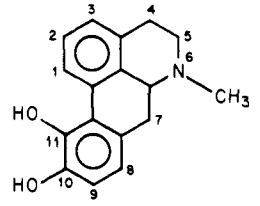
Synthesis and Evaluation of 1,2,3,4-Tetrahydro[1]benzothieno[2,3-*h*]isoquinolines as Dopamine Antagonists

Charles R. Ellefson* and Kathleen A. Prodan

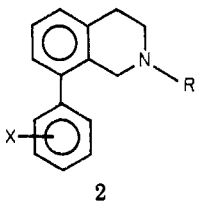
G. D. Searle and Company, Chicago, Illinois 60680. *Received February 9, 1981*

1,2,3,4-Tetrahydro[1]benzothieno[2,3-*h*]isoquinolines were prepared and evaluated as dopamine antagonists and for potential neuroleptic activity. These compounds, which are analogues of the dopamine agonist apomorphine (**2**) in which the C-7 methylene has been removed, were found to be dopamine antagonists by in vitro receptor binding studies. However, in vivo evaluation did not suggest potential antipsychotic activity.

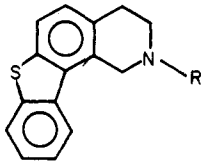
In previous reports[1,2] we have described the synthesis and biological evaluation of some 8-aryl-1,2,3,4-tetrahydroisoquinolines, **2**, which are ring-opened analogues of



1



2



3

apomorphine (**1**). In contrast to **1**, the 8-aryl group of **2** is free to rotate out of general planarity with the rest of the molecule. Those compounds were found to be potent inhibitors of dopamine by in vitro dopamine receptor assays. In vivo evaluation of their biological effects did not indicate potential usefulness as antipsychotic agents, however.

This report describes the synthesis and evaluation of 1,2,3,4-tetrahydro[1]benzothieno[2,3-*h*]isoquinoline derivatives, **3**, which are also analogues of **1** in which the C-7 methylene group is absent. The two aromatic rings of **3** are held in a planar orientation by a sulfur bridge and, therefore, the overall geometry may more closely resemble **1**. Our objective was to determine if planar molecules such as **3** would have greater in vivo effects than the freely rotating compounds, **2**.

Chemistry. Synthesis of the title compounds is outlined in Scheme I. Dibenzothiophene-1-carboxylic acid (**4**) was prepared from 2-allylbenzo[*b*]thiophene and ethyl dichloroethoxyacetate[3] according to published methods.[4] It was converted to the acid chloride and reacted with 2-amino-2-methylpropanol, yielding an hydroxyamide. Cyclization with thionyl chloride produced the oxazoline **5**. Treatment of **5** with *n*-butyllithium, followed by ethylene oxide, produced **6**. The alcohol was converted to the lactone **7** by refluxing with 6 N hydrochloric acid. Heating **7** with benzylamine hydrobromide in benzylamine at 160 °C opened the lactone to the hydroxyamide **8**. The alcohol of **8** was converted to the mesylate, which on treatment with sodium hydride was cyclized to the dihydroisoquinolinone **9**. Lithium aluminum hydride reduction of **9** produced *N*-benzyl-1,2,3,4-tetrahydro[1]benzothieno-[2,3-*h*]isoquinoline **10**.

(1) C. R. Ellefson, *J. Org. Chem.*, **44**, 1533 (1979).
(2) C. R. Ellefson, K. A. Prodan, L. R. Brougham, and A. Miller, *J. Med. Chem.*, **23**, 977 (1980).
(3) R. G. Jones, *J. Am. Chem. Soc.*, **73**, 5168 (1951).
(4) J. Ashby, M. Ayad, and O. Meth-Cohn, *J. Chem. Soc., Perkin Trans. 1*, 1744 (1974).

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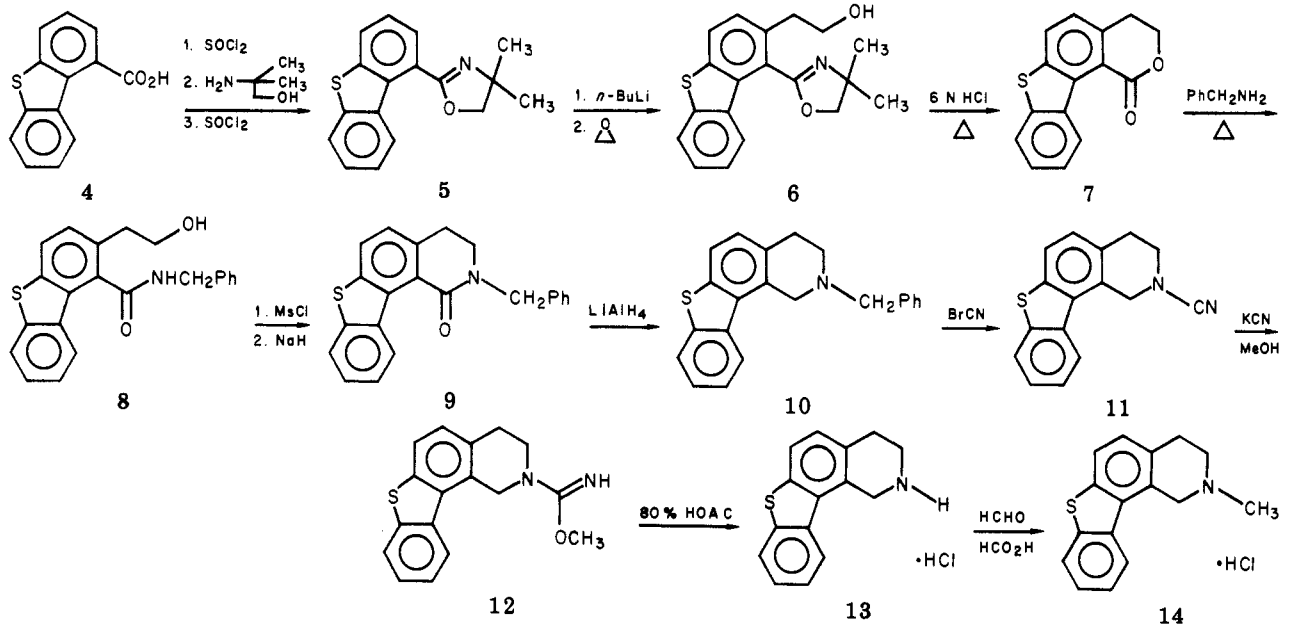
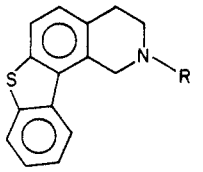
Scheme I



4 5 6 7 8 9 10 11 12 13 14

Table I. Biological Evaluation of 9-14



compd	R	IC_{50},[a] M [^{3}H]DA	IC_{50},[a] M [^{3}H]HP	ratio[b]	CAR[c]	rel CNS act.[d]	LD_{50}, mg/kg
9	CH_2Ph, 1-oxo	$>10^{-4}$	4.5×10^{-6}		I (10, 40)	NT	>320
10	CH_2Ph·HCl	$>10^{-4}$	7.5×10^{-7}		I (10, 40)	–	>320
11	CN	2.2×10^{-4}	1×10^{-5}	22	NT[e]	NT	NT
12	$C(OCH_3)=NH$	9.6×10^{-6}	5×10^{-7}	19	NT	NT	NT
13	H·HCl	$>10^{-4}$	2.1×10^{-5}		I (10, 40)	+++	<320
14	CH_3·HCl	7×10^{-6}	8.4×10^{-7}	8.3	A (40), I (10)[f]	++	>80
2[g]	X = H, R = CH_3	6.6×10^{-5}	2.7×10^{-8}	2400	A (40), I (10)	+++	>320
chlorpromazine		2.5×10^{-6}	3.4×10^{-8}	74		+++	
clozapine		8×10^{-6}	1.8×10^{-7}	44		+++	
haloperidol		5×10^{-7}	1.8×10^{-9}	278		+++	

[a] Drug concentrations which inhibit specific binding of 5 nM [^{3}H]dopamine or 1.6 nM [^{3}H]haloperidol by 50%. [b] IC_{50} ([^{3}H]DA)/IC_{50} ([^{3}H]HP). [c] Conditioned avoidance response in trained rat (CAR). Active (A) or inactive (I) at the doses (mg/kg) indicated. [d] See ref 2 for explanation and description of assays; see ref 6 for definition of abbreviations. Relative CNS activity was rated as follows: +++, activity in ≥6 assays; ++, activity in 4–5 assays; +, activity in 2–3 assays; –, activity in ≤1 assay. Activities shown or inactivity (I) at the designated doses were observed as follows: 10, I (64, 3); 13, Ma, St, He, Ho, Ta, Ro (64), I (4); 14, Ma, St, Ta, Mo, Am (32), I (2); 2, Ma, St, He, Ho, Ta, Ro (64), I (3); chlorpromazine, St, Ho, Ta, Ro (36), He, Se (36, 2), Am (2); haloperidol, He, Ho, Ta, Se (20), Ro, Am (20, 2), Me (2); clozapine, He, Ho, Se, Ro, Am (10), Ta (10, 1). [e] NT = not tested. [f] Depression was observed at the 40 mg/kg dose. [g] This is compound 12a of ref 2.

Attempts to debenzylate **10** by catalytic hydrogenolysis gave only very low yields of **13**, probably due to sulfur poisoning of the catalyst. A more productive route to **13** was found by going through the cyanamide **11**. Treatment of **10** with cyanogen bromide in a von Braun reaction effected the loss of the *N*-benzyl group to produce **11**. Removal of the *N*-cyano function was accomplished in a two-step process[5] by first reacting **11** with potassium cyanide in methanol to yield the imidoate **12**, which was converted to 1,2,3,4-tetrahydro[1]benzothieno[2,3-*h*]isoquinoline **13** on hydrolysis with 80% acetic acid. Eschweiler–Clarke reaction of **13** produced the *N*-methyl compound **14**.

(5) A. Donetti and E. Bellora, *J. Org. Chem.*, **37**, 3352 (1972).

Biological Results

The assays used[6] for the biological evaluation were described and discussed in detail in ref 2. A discussion of

(6) These were dopamine receptor binding studies, conditioned avoidance response in trained rat (CAR), LD_{50}, and relative CNS activity as evaluated in a battery of 16 standard assays. Activities observed in the CNS battery are abbreviated in Table I as follows: Ma, antagonism of minimal electroshock seizures; St, antagonism of strychnine-induced seizures; He, potentiation of barbiturate sleeping time; Ho, analgesia (hot-plate test); Ta, analgesia (tail-clip test); Ro, rotating-rod test for motor coordination; Mo, antagonism of morphine-induced analgesia; Am, inhibition of amphetamine-induced lethality; Se, antagonism of serotonin-induced diarrhea; Me, antagonism of metrazole-induced seizures.

the evaluation of compounds 9–14 is presented herein and summarized in Table I.

The compounds were first evaluated in vitro in the dopamine receptor binding assay for their ability to displace [^{3}H]dopamine ([^{3}H]DA) and [^{3}H]haloperidol ([^{3}H]HP). The results indicated that all of the compounds were dopamine antagonists;[7] i.e., they were all more potent displacers of [^{3}H]HP than [^{3}H]DA. Compound 14 was active in the same range as the 8-aryltetrahydroisoquinolines, but it was not as active as the more active compounds of that group (compound 2 of Table I, for example). Even compounds 11 and 12 with electronegative groups on the nitrogen appear to have some ability to interact with the dopamine receptor.

The compounds were evaluated in vivo for their effects on conditioned avoidance response (CAR) behavior in trained rats and in a battery of 16 standard assays for potential central nervous system (CNS) effects. Only compound 14 had an effect on CAR behavior in rats. However, at the active dose, 40 mg/kg, depression was also observed. In the battery of 16 assays for CNS effects, compounds 13 and 14 showed activity only at the higher dose, and only 13 had three activities similar to the six common activities (He, Ho, Ta, Se, Ro, and Am) of the standard compounds. Compound 14 did have activity against amphetamine lethality, but protection was only observed at the high dose (32 mg/kg).

A comparison of compounds 13 and 14 with the 8-aryltetrahydroisoquinolines[2] (2) shows that the rigid structure imposed by the sulfur bridge has not produced the desired effect (greater in vivo activity). Our results indicate that compounds of general structure 3 are, indeed, dopamine antagonists by in vitro assay, but they do not show any enhanced activity (either in vitro or in vivo) compared to 2. This possibly indicates that the freely rotating 8-aryl group of 2 can adopt an angle of twist of the biphenyl portion of the molecule that is closer to the skewed angle in apomorphine.[8] The planarity of 3 seems to make it worse, i.e., decreased activity was observed.

Experimental Section

NMR (Varian A-60D) and IR (Beckman IR-12) spectra were consistent with all of the assigned structures. Analytical results when indicated by symbols for the elements were within 0.4% of the theoretical values. Melting points were determined in open capillary tubes in a Mel-Temp apparatus and are uncorrected.

2-(1-Dibenzothienyl)-4,5-dihydro-4,4-dimethyloxazole (5). A mixture of 50 g (0.22 mol) of dibenzothiophene-1-carboxylic acid[4] and 175 mL of thionyl chloride was stirred overnight. The excess thionyl chloride was stripped off and the residue was dissolved in 225 mL of methylene chloride and added to a solution of 39.1 g (0.438 mol) of 2-amino-2-methyl-1-propanol in 225 mL of methylene chloride. After 3 h the solid was collected by filtration, washed with water, and air-dried to yield 56.0 g (86%) of a cream-colored solid. Recrystallization from chloroform/hexane and ethyl acetate gave analytical samples of *N*-(1,1-dimethyl-2-hydroxyethyl)-1-dibenzothiophenecarboxamide, mp 179.5–182 °C.

Thionyl chloride (45 mL) was added in portions to 36 g (0.12 mol) of the hydroxyamide. The mixture was stirred until solution was achieved and then poured into 850 mL of ether. The resulting solid was filtered off and suspended in water, and the solution was made basic with concentrated ammonium hydroxide. The solid was washed with water to yield 30.5 g (89%), mp 111.5–113.5 °C. Recrystallization from ethyl acetate/hexane gave mp 112–113.5 °C; IR ($CHCl_3$) 1663 cm^{-1}; NMR ($CDCl_3$) δ 1.51 (s, 6 H), 4.22 (s, 2 H), 7.19–8.55 (m, 7 H). Anal. ($C_{17}H_{15}NOS$) C, H, N.

1-(4,5-Dihydro-4,4-dimethyloxazol-2-yl)-2-dibenzothiopheneethanol (6). *n*-Butyllithium (15 mL of 2.6 M in hexane) was added to 7.4 g (0.026 mol) of 5 in 200 mL of dry tetrahydrofuran at <0 °C under nitrogen. After 0.5 h the mixture was warmed to ambient temperature for 1.5 h. Ethylene oxide (12 mL) in 12 mL of tetrahydrofuran was added and stirred overnight. Water (25 mL) was added dropwise, the tetrahydrofuran was distilled off, and the residue, taken up in ether, was washed (H_2O) and dried ($MgSO_4$). Removal of the solvent gave 9.5 g of semisolid that was chromatographed on silica gel with ethyl acetate/toluene to yield 4.0 g of pale yellow solid. Recrystallization from ethyl acetate/hexane gave pale yellow-orange crystals: mp 149–151.5 °C; IR ($CHCl_3$) 3270 (br), 1655 cm^{-1}; NMR ($CDCl_3$) δ 1.54 (s, 6 H), 3.00 (t, J = 6 Hz, 2 H), 3.88 (t, J = 6 Hz, 2 H), 4.31 (s, 2 H), 7.23–8.12 (m, 6 H). Anal. ($C_{19}H_{19}NO_2S$) C, H, N.

3,4-Dihydro[1]benzothieno[2,3-*h*][2]benzopyran-1(1*H*)-one (7). A mixture of 7.3 g (0.022 mol) of 6 and 750 mL of 6 N HCl was stirred at gentle reflux for 2.5 h. The solid (5.16 g) was collected, washed with water, and recrystallized from acetonitrile to yield 3.1 g of beige crystals: mp 154.5–155 °C (plus a second crop of 0.95 g, mp 152–154 °C); 71% total yield; IR ($CHCl_3$) 1721 cm^{-1}; NMR ($CDCl_3$) δ 3.05 (t, J = 5.5 Hz, 2 H), 4.45 (t, J = 5.5 Hz, 2 H), 7.08–7.97 (m, 5 H), 8.75–9.13 (m, 1 H). Anal. ($C_{15}H_{10}O_2S$) C, H.

2-(2-Hydroxyethyl)-*N*-(phenylmethyl)-1-dibenzothiophenecarboxamide (8). A mixture of 9.7 g (0.038 mol) of 7 and 10 g of benzylamine hydrobromide in 30 mL of benzylamine was stirred at 175 °C for 3 h. The mixture was poured into 600 mL of 5% hydrochloric acid. The solid was washed with 5% hydrochloric acid and water to yield 13.4 g (97%) of beige powder. An analytical sample was obtained by repeated recrystallizations from 2-propanol and ethyl acetate/hexane: mp 125–138 °C; IR ($CHCl_3$) 3640, 3435, 3350 (br), 1660 cm^{-1}; NMR ($CDCl_3$) δ 2.50 (br, 1 H), 2.79 (t, J = 6 Hz, 2 H), 3.72 (t, J = 6 Hz, 2 H), 4.62 (d, J = 5.5 Hz, 2 H), 6.73–8.05 (m, 11 H). Anal. ($C_{22}H_{19}NO_2S$) C, H, N.

3,4-Dihydro-2-(phenylmethyl)[1]benzothieno[2,3-*h*]isoquinolin-1(1*H*)-one (9). A solution of 8.8 g (0.024 mol) of 8 and 5.8 g (0.050 mol) of mesyl chloride in 90 mL of pyridine was kept in a refrigerator overnight. The mixture was poured into 500 mL of ice–water, and the solid that formed was washed with water to yield 10.2 g of the mesylate: mp 140–143 °C.

A solution of 3.5 g (0.073 mol) of 50% sodium hydride and 10.1 g of the mesylate in 200 mL of dry tetrahydrofuran was refluxed overnight. Water was added and the tetrahydrofuran was distilled off. The residue was dissolved in methylene chloride, washed with water, 5% HCl, and 5% NaOH, and dried. Removal of the solvent gave a residue that was triturated with ether to remove the residual mineral oil to yield 7.7 g of solid, which was purified by Soxhlet extraction using hexane as the solvent. Cooling the extraction solution yielded 6.4 g (82%) of white crystals: mp 118.5–119.5 °C; IR ($CHCl_3$) 1645 cm^{-1}; NMR ($CDCl_3$) δ 2.70–3.05 (m, 2 H), 3.29–3.64 (m, 2 H), 4.88 (s, 2 H), 7.01–7.98 (m, 10 H), 8.80–9.27 (m, 1 H). Anal. ($C_{22}H_{17}NOS$) C, H, N.

1,2,3,4-Tetrahydro-2-(phenylmethyl)[1]benzothieno[2,3-*h*]isoquinoline Hydrochloride (10). Lithium aluminum hydride (4.0 g, 0.01 mol) was added to 11.9 g (0.035 mol) of 9 in 400 mL of dry tetrahydrofuran and refluxed for 3 h. After cooling, the mixture was decomposed with (1) 8 mL of water in 16 mL of tetrahydrofuran, (2) 8 mL of 25% sodium hydroxide, and (3) 8 mL of water. The salts were filtered off, and the solvent was distilled to yield 13.0 g of a thick oil. The oil was taken up in ether and treated with 2-propanolic hydrogen chloride to yield 11.9 g (94%) of light yellow powder. Recrystallization (MeOH and HOAc) gave white crystals: mp 251–256 °C; NMR of the free amine ($CDCl_3$) δ 2.50–3.09 (m, 4 H), 3.73 (s, 2 H), 4.15 (s, 2 H), 6.73–8.07 (m, 11 H). Anal. ($C_{22}H_{20}ClNS$) C, H, N.

3,4-Dihydro[1]benzothieno[2,3-*h*]isoquinoline-2(1*H*)-carbonitrile (11). A mixture of 6.8 g (0.021 mol) of the free amine (10) and 2.7 g (0.026 mol) of cyanogen bromide in 250 mL of anhydrous ether was stirred at reflux overnight. The solid that separated on cooling was collected, yielding 4.9 g (89%) of yellow

(7) I. Creese, D. R. Burt, and S. H. Synder, *Life Sci.*, 17, 993 (1975).

(8) X-ray analysis of the aporphine, bulbocapnine methiodide, has shown that the angle of twist of the biphenyl portion was 29.9°. See M. Shamma, "The Isoquinoline Alkaloids", Academic Press, New York, 1972, p 210.

crystals. Recrystallization from ethanol gave colorless needles: mp 140–140.5 °C; IR ($CHCl_3$) 2210 cm^{-1}; NMR ($CDCl_3$) δ 2.98–3.72 (m, 4 H), 5.03 (s, 2 H), 7.06–8.20 (m, 6 H). Anal. ($C_{16}H_{12}N_2S$) C, H, N.

Methyl 3,4-Dihydro[1]benzothieno[2,3-*h*]isoquinoline-2(1*H*)-methanimidoate (12). A mixture of 4.6 g (0.018 mol) of 11 and 1.1 g (0.018 mol) of potassium cyanide in 50 mL of methanol was stirred for 4 h at reflux and overnight at ambient temperature. The solvent was distilled off and the residue partitioned between water and ethyl acetate. The organic portion was washed (H_2O) and dried ($MgSO_4$); removal of the solvent yielded 5.0 g (96%) of a tan solid; recrystallization of 100 mg from ethyl acetate/hexane gave 90 mg of pale yellow crystals: mp 128.5–130 °C; IR ($CHCl_3$) 3380, 1633 cm^{-1}; NMR ($CDCl_3$) δ 3.02 (t, J = 5.5 Hz, 2 H), 3.70 (t, J = 5.5 Hz, 2 H), 3.80 (s, 3 H), 4.93 (br, 1 H), 5.14 (s, 2 H), 7.10–8.37 (m, 6 H). Anal. ($C_{17}H_{16}N_2OS$) C, H, N.

1,2,3,4-Tetrahydro[1]benzothieno[2,3-*h*]isoquinoline Hydrochloride (13). A solution of 4.8 g (0.016 mol) of 12 in 50 mL of 80% acetic acid was stirred at reflux overnight. It was poured into 300 mL of water, made basic with 50% sodium hydroxide, and extracted with ether. The ether solution was dried ($MgSO_4$) and concentrated to yield 3.8 g of yellow solid. This solid was dissolved in ethanol and treated with 2-propanolic hydrogen chloride to yield 3.3 g (73%) of pale yellow powder. Recrystallization from glacial acetic acid/water gave white crystals: mp >300 °C; NMR of free amine ($CDCl_3$) δ 1.92 (s, 1 H), 2.71–3.35 (m, 4 H), 4.64 (s, 2 H), 7.06–8.40 (m, 6 H). Anal. ($C_{15}H_{14}ClNS$) C, H, N.

2-Methyl-1,2,3,4-tetrahydro[1]benzothieno[2,3-*h*]isoquinoline Hydrochloride (14). A mixture of 1.7 g (0.007 mol) of 13 (free amine), 0.88 g of 90% formic acid, and 0.65 g of 37% formaldehyde was stirred at ambient temperature overnight and warmed on a steam bath for 5 h. Concentrated hydrochloric acid (0.75 mL) was added and then water, and the mixture was made basic with 50% sodium hydroxide, extracted with ether, washed (H_2O), and dried ($MgSO_4$). Removal of the ether gave 1.7 g (94%) of white solid, which was redissolved in ether and treated with 2-propanolic hydrogen chloride. The white powder was recrystallized from glacial acetic acid to yield 1.7 g (80%) of white crystals: mp 257–262 °C; NMR of free amine ($CDCl_3$) δ 2.59 (s, 3 H), 2.45–3.22 (m, 4 H), 4.17 (s, 2 H), 7.06–8.22 (m, 6 H). Anal. ($C_{16}H_{16}ClNS$) C, H, N.

Acknowledgment. The authors express their appreciation to James Bloss for biological data, to Linda Brougham and Arni Miller for dopamine receptor data, to Aristides Damascus for spectra, to Emanuel Zielinski for microanalyses, and to Karen Macali for help in preparation of the manuscript.

Book Reviews

Advances in Biochemical Psychopharmacology. Volume 29. Amino Acid Neurotransmitters. By Francis V. DeFeudis and Paul Mandel. Raven Press, New York. 1981. xxviii + 512 pp. 16 × 24 cm. $59.00.

This volume represents the proceedings of a symposium that was held on July 10 and 11, 1980, in Colmar, France, as a satellite to the 28th International Congress of Physiological Sciences. This volume presents approaches to the understanding of amino acid actions from many biological disciplines, including physiology, morphology, pharmacology, and biochemistry. Particular emphasis is placed on the roles of amino acids in integrated central nervous system functions and behavior, receptor pharmacology at both in vivo (electrophysiological) and in vitro (ligand binding) levels, amino acid uptake and release, enzymology, metabolism, and autoradiographic studies.

This volume should facilitate further research in this area and would improve our understanding and therapeutic management of many human neuropsychiatric disorders, including epilepsy and parkinsonism. It will be of interest primarily to biological scientists, clinicians, and to those medicinal chemists who wish to increase their knowledge on amino acid neurotransmitters.

Staff

Marijuana. The First Twelve Thousand Years. By Earnest L. Abel. Plenum Press, New York. 1980. xi + 289 pp. 16 × 23.5 cm. $17.95.

LSD. My Problem Child. By Albert Hofmann. Translated by Jonathan Ott. McGraw-Hill, New York. 1980. xiii + 210 pp. 14 × 21.5 cm. $9.95.

Here are two small, very well written books on the histories of two of our most interesting psychoactive drugs, one ancient, one modern; one natural, the other synthetic; and both controversial.

In recent years, much of what has been written in the scientific and lay press about the social, political, legal, chemical, pharmacological, and medicinal concerns connected with the use and abuse of *Cannabis* has done little more than confirm that "Those who cannot remember the past are condemned to repeat it." Our age is certainly not the first to attempt to deal with these problems. Abel's book is a balanced, well-documented review of the facts, the myths, and the legends surrounding the religious, economic, and medicinal history of one of Man's ancient and most useful cultivated plants. It contains but a smattering of chemistry and pharmacology as well as a brief reference to the modern medicinal potential of THC and its derivatives; yet no one with even a peripheral interest in the impact of *Cannabis* on our society—scientists, parents, teachers, social workers, and the legal profession—should miss this very readable account of all that has gone before.

Hofmann's "problem child", not yet 50 years of age—closer to 40 for all practical purposes and a test-tube baby at that—brought fame to its parent and honor to his house, yet terror and trouble to much of the rest of the neighborhood once it learned to get around. Will it ever grow up? If father does know best, there is hope. With considerable soul searching, the author analyzes his own experiences with LSD and psilocybin, those of his colleagues, friends, and acquaintances, as well as Man's historical search for the mystical experience, in an attempt to answer the question, to find the proper place for these potent psychoactive agents in contemporary society. They are not, he concludes, for everybody: Crossing the line between reality and Reality (if one be permitted to put it that way) carries risks along with its potential rewards and the risks are not yet all that well-known. The translator is to be congratulated in capturing the sense of awe and wonder with which Hofmann regards his child, problem or not.

Northeastern University
Boston, Massachusetts 02115
Robert F. Raffauf

Isotopes: Essential Chemistry and Applications. By J. A. Elvidge and J. R. Jones. Royal Society of Chemistry, London. 1980. xii + 400 pp. 20.8 × 14.7 cm. $32.50.

Today the safe and informative exploitation of the stable and radioactive isotopes of C, H, N, O, P, and S is widespread, especially in the life sciences. This text dealing with the chemistry