Synthesis of Ketoximino-Esters as Potential Ataraxics

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A series of oximino-esters of 1-phenyl-1,2-propanedione-2-oxime, 10,11-dihydrodibenzo[*a,d*]cyclohepten-5-one oxime, 3-benzoylindole oxime, 9-fluorenone oxime, and benzophenone oxime were prepared. The respective ketones were oximinated in pyridine with hydroxylamine hydrochloride. The esterification was conducted in either benzene or ether with equimolar quantities of acylchloride, oxime, and a basic reagent. In this investigation, 16 new oximino-esters were synthesized. The pharmacological screening revealed that these agents with appropriate pharmacophores exhibit ataractic activity. The diphenylcarbamyl analogs showed the most significant tranquilizer effectiveness.

In the last decade, many structurally different tranquilizers have been introduced. Mechanisms of pharmacological action have not been established definitively for drugs in this category, but the structural diversity among these compounds suggests many different central nervous system sites and actions. Drugs used in therapy of psychoses—phenothiazines and rauwolfia alkaloids—seem to differ considerably in general pattern from those such as the propanediols which are used in the treatment of common neuroses and tension (1). However, the actions of these two major tranquilizers (phenothiazines and reserpine) are sufficiently different at several points to allow the conclusion that the state of tranquility which each drug induces is reached by a different pharmacological route. Thus, the review of the studies of the actions of these drug groups by some workers has led to the postulation that rauwolfia tranquilizers activate the trophotropic system and phenothiazines block the ergotropic system (2). Nieforth (3), on the other hand, believes that there may be only one site of action for these two drug groups.

Within the phenothiazine related groups, there are indications of differences of activity. Compounds such as 5-(3-dimethylaminopropyl)-10,11-dihyrodibenz[*b,f*]azepine (imipramine) and 5-(3-dimethylaminopropylidine)-10,11-dihydrodibenz[*a,d*]cycloheptadiene (amitriptyline) show some similarity and dissimilarity in pharmacological activity from the typical phenothiazine tranquilizer. Monro (4) believes that the differences in pharmacological action may be due to the nonconjugation and conjugation of benzene rings in imipramine and promazine, respectively. A study of the literature also revealed that most of the major tranquilizers possess a two or three carbon distance between the ring and the nitrogen of the amine, indicating that this distance may be critical in drug–receptor interaction.

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In consideration of these physicochemical points, a study of the effects of the carbon bridge in the imipramine type of molecule by selection of compounds with or without the bridge and a study of the influence of the two or three carbon chain were suggested. This is accomplished by replacing the bridge in the imipramine type of molecule and by replacing the two or three carbon chain by oximino-esters. The oximino linkage will affect the partition coefficient, stereochemistry, and metabolic degradation of these compounds. With this in mind, the authors have synthesized oximino-esters of 10,11-dihydrodibenzo[*a,d*]cyclohepten-5-one oxime, 9-fluorenone oxime, benzophenone oxime, 3-benzoylindole oxime, and 1-phenyl-1,2-propanedione-2-oxime. The physical constants for these esters are shown in Table I.

EXPERIMENTAL[1]

Synthesis of Oximes

10,11 - Dihydrodibenzo[a,d]cyclohepten - 5 - one Oxime.—10,11 - Dihydrodibenzo[*a,d*]cyclohepten-5-one (75 Gm., 0.36 mole), and hydroxylamine hydrochloride (75 Gm., 1.08 moles) in pyridine (1.12 L.) were refluxed according to the method of Monro *et al.* (4). The oxime exhibited a melting point of 167–169°. [Lit. m.p. 166–169° (4).] The yield was 50 Gm. (61%).

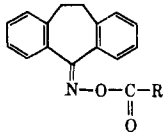
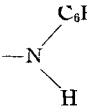
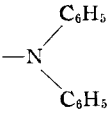
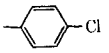
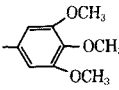
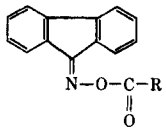
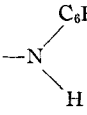
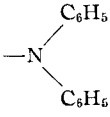
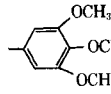
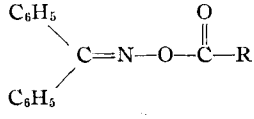
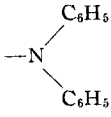
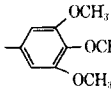
9-Fluorenone Oxime.—9-Fluorenone (9.0 Gm., 0.05 mole), hydroxylamine hydrochloride (9.0 Gm., 0.13 mole), and potassium hydroxide (7.3 Gm., 0.13 mole), in ethanol (150 ml.) were heated under reflux for 7 hr. The bulk of the ethanol was removed under reduced pressure and the mixture poured into the cold water. The crude product thus obtained was recrystallized from benzene which afforded the pure oxime, m.p. 194°. [Lit. m.p. 187–188° (8).]

Benzophenone Oxime.—This product was prepared according to the method reported in "Organic Syntheses" (9). The yield was 80% of the theoretical, m.p. 143–145°.

3-Benzoylindole Oxime.—3-Benzoylindole (8.8 Gm., 0.04 mole), hydroxylamine hydrochloride (6.9 Gm., 0.10 mole), and pyridine (75 ml.) in

[1] Reported melting points are uncorrected. A Thomas-Hoover Unimelt apparatus was used for melting point determination. Schwarzkopf Microanalytical Laboratory, Woodside, N. Y., conducted the elemental analyses.

TABLE I.—PHYSICAL CONSTANTS AND ANALYTICAL DATA

Compd.	R	Method of Prepn.	M.p., °C.	Recrystn. Solvent	% Yield	Empirical Formula	Anal. % Calcd.	Anal. % Found
								
I		*A*	214–215 dec.	Benzene	61.0	$C_{22}H_{18}N_2O_2$	C, 77.17 H, 5.29	C, 77.19 H, 5.44
II		*B*	150–151 dec.	Ethanol	60.0	$C_{28}H_{22}N_2O_2$	C, 80.35 H, 5.29	C, 80.05 H, 5.20
III		*C*	133–134	Ethanol–propanol	42.0	$C_{22}H_{16}ClNO_2$	C, 73.03 H, 4.46	C, 73.03 H, 4.58
IV		*D*	185–186	Benzene	74.0	$C_{25}H_{23}NO_5$	C, 71.92 H, 5.55	C, 72.15 H, 5.45
								
V		*A*	166–167 dec.	Benzene	68.0	$C_{20}H_{14}N_2O_2$	C, 76.42 H, 4.48	C, 76.59 H, 4.42
VI		*B*	209–210 dec.	Ethanol	70.0	$C_{26}H_{18}N_2O_2$	C, 79.98 H, 4.65	C, 80.09 H, 4.67
VII		*D*	168	Methanol–ethanol	58.0	$C_{23}H_{19}NO_5$	C, 71.20 H, 4.91	C, 70.33 H, 4.78
								
VIII		*B*	165–166 dec.	Ethanol	52.0	$C_{26}H_{20}N_2O_2$	C, 79.56 H, 5.14	C, 79.31 H, 5.35
IX		*D*	129–130	Ethanol	65.0	$C_{23}H_{21}NO_5$	C, 70.57 H, 5.41	C, 70.52 H, 5.62

dimethylsulfoxide (20 ml.) were heated under reflux for 24 hr. The pyridine was removed under vacuum, and the residue was poured in cold water. The crude material was recrystallized from ethanol–propanol to yield 2.36 Gm. (25%) of a pure sample, m.p. 192–193°.

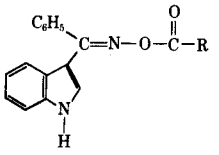
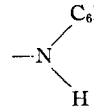
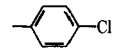
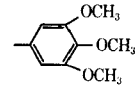
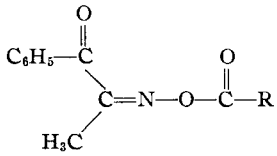
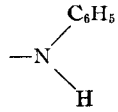
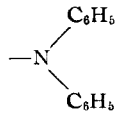
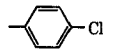
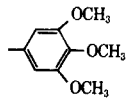
Anal.—Calcd. for $C_{15}H_{12}N_2O$: C, 76.24; H, 5.12. Found: C, 76.51; H, 5.31.

Synthesis of Oximino-Esters[2]

5- (Phenylcarbamyloximino)- 10,11 - dihydro - 5H-dibenzo[a,d]cycloheptene (I).—*Method A.*—10,11-Dihydrodibenzo[*a,d*]cyclohepten-5-one oxime (2.23 Gm., 0.10 mole), and phenylisocyanate (1.2 Gm., 0.01 mole) in pyridine (0.8 Gm., 0.01 mole) were

[2] See Table I for physical constants and analytical data.

TABLE I.—CONTINUED

Compd.	R	Method of Prepn.	M.p., °C	Recrystn. Solvent	% Yield	Empirical Formula	Anal. % Calcd.	Anal. % Found
								
X		*A*	243 dec.	Ethanol	58.0	$C_{22}H_{17}N_3O_2$	C, 74.34 H, 4.82	C, 74.12 H, 5.81
XI		*C*	174–175 dec.	Methanol	18.0	$C_{22}H_{15}ClN_2O_2$	C, 70.49 H, 4.04	C, 70.29 H, 4.16
XII		*D*	169–170	Benzene	25	$C_{25}H_{22}N_2O_5$	C, 69.75 H, 5.15	C, 69.76 H, 5.08
								
XIII		*A*	147	Ethanol	70	$C_{16}H_{14}N_2O_3$	C, 68.08 H, 4.99	C, 68.31 H, 4.83
XIV		*B*	132–133 dec.	Benzene	65	$C_{2}H_{18}N_2O_3$	C,73.72 H, 5.06	C, 73 48 H, 4.85
XV		*C*	105–107	Methanol	22	$C_{16}H_{12}ClNO_3$	C, 63.68 H, 4.01	C, 63.82 H, 4.25
XVI		*D*	145–146	Ethanol	35	$C_{19}H_{19}NO_6$	C, 63.85 H, 5.35	C, 63.66 H, 5.19

heated in a conical flask, protected with a drying tube, on a steam bath for 30 min. according to the method of Kochhar *et al.* (5). Repeated crystallization from benzene afforded the pure product, m.p. 214–215°; yield 61%.

9 - (Diphenylcarbamyloximino)fluorene (VI).—*Method B.*—9-Fluorenone oxime (1.95 Gm., 0.01 mole), diphenylcarbamyl chloride (2.31 Gm., 0.01 mole), and pyridine (1.0 Gm., 0.012 mole) in 200 ml. anhydrous benzene were refluxed for 5 hr. The solution was filtered and the benzene washed with 10% potassium bicarbonate (20-ml. portion) five times. It was then washed with water (20-ml. portion) ten times. The benzene layer was dried over anhydrous sodium sulfate and evaporated under reduced pressure. The solid residue obtained was crystallized from ethanol to give yellow needles (70% yield), m.p. 209–210°.

5- (p- Chlorobenzoyloximino)- 10,11- dihydro- 5H- dibenzo[a,d]cycloheptene (III).—*Method C.*—With slight modifications, the procedure of Gass and Bope (6) was used in this preparation. 10,11-Dihydrodibenzo[*a,d*]cyclohepten-5-one oxime (2.23 Gm., 0.01 mole), *p*-chlorobenzoylchloride (1.75 Gm., 0.01 mole), pyridine (0.79 Gm., 0.01 mole) in 50 ml. of anhydrous ether were stirred at room temperature for 2 hr. The ether was evaporated, and the solid residue was washed seven times with 10% K_2CO_3 (20-ml. portion) and then ten times with cold water. The light yellow solid upon recrystallization from ethanol–propanol gave white crystals; yield, 1.5 Gm. (42%), m.p. 133–134°.

5 - (3,4,5 - Trimethoxybenzoyloximino) - 10,11-dihydro - 5H - dibenzo[a,d]cycloheptene (IV).—*Method D.*—This compound was prepared from 10,11-dihydrodibenzo[*a,d*]cyclohepten-5-one oxime by esterification according to the method described by Counsell and Soine (7) with slight modification. Pyridine was used to facilitate the esterification. The crude residue recrystallized from benzene yielded a pure white crystalline sample, m.p. 185–186°; yield 74%.

TABLE II.—ANTISEROTONIN AND ANTIAMPHETAMINE ACTIVITY OF KETOXIMINO-ESTERS IN MICE

Compd.	Antiserotonin Activity			Antiamphetamine Activity		
	Mice, No.	Dose, mg./Kg.	Twitches, No.	Mice, No.	Dose, mg./Kg.	% Mortality
I	6	100	6[a]	6	150	100
				6	100	0[a]
II	6	100	0[a]	6	100	33 1/3[a]
III	6	100	3[a]	6	100	50
IV	6	50	29			
	6	100	0[a]	6	50	66 2/3
V	6	100	13	5	100	20[a]
VI	6	100	19			
VII	6	100	2[a]	6	75	33 1/3[a]
VIII	6	100	17	6	100	66 2/3
IX	6	100	13	6	100	16 2/3[a]
XII	6	100	6[a]			
XIII	6	100	12	6	100	50
XIV	6	100	8	6	100	0[a]
XV	6	100	4[a]	6	100	66 2/3
XVI	6	100	18	6	100	16 2/3[a]
Prochlorperazine	6	2.5	0[a]	6	2.5	0[a]
Control	6		23	12		58 1/3

[a] Significantly less than control value at 5% probability.

PHARMACOLOGY

Preliminary screening for ataractic activity employed two techniques: (*a*) the procedure of Corne *et al.* (10) which measures the blocking of 5-hydroxytryptophane induced head twitches in mice and (*b*) the method of Lapin (11) in which tranquilizer activity is based on reduction of lethality of amphetamine in grouped mice.

All the test drugs were administered intraperitoneally in acacia suspension within a dose range of 50–150 mg./Kg. All injections were made 30 min. prior to the challenge injection of 5-hydroxytryptophane or amphetamine. The amphetamine was administered subcutaneously in a dose of 20 mg./Kg. and the 5-hydroxytryptophane intraperitoneally in a dose of 300 mg./Kg. Conclusions as to tranquilizer activity were based on reduction of serotonin induced twitches and reduction of mortality in grouped amphetamine-dosed mice as compared with controls in each test. 2-Chloro-10-[3-(1-methyl-4-piperazinyl)-propyl]phenothiazine (prochlorperazine) was used for comparison control. Results are presented in Table II.

Toxicity was evident in the administration of compound I at 150 mg./Kg. and compound VII at 100 mg./Kg. Deaths attributable evidently to test drugs occurred in these groups.

STRUCTURE-ACTIVITY RELATIONSHIPS

Pharmacological screening revealed that phenylcarbamyloximino derivatives, compounds I and V, do exhibit ataractic activity. Compound I reduced the hyperserotonin twitches and protected mice from amphetamine. These observations indicate that conjugation of the benzene rings as well as the dimethylaminopropyl group of many phenothiazine derivatives are not essential for tranquilizing activity. These observations were further substantiated by testing other oximino-esters. The diphenylcarbamyloximino analogs of compounds II and XIV showed considerable ataractic activity, indicating that the size of the aralkyl group on the nitrogen of the side chain might be effectively blocking the receptor site.

The *p*-chlorobenzoyloximino derivatives of III and XV were effective against antiserotonin activity. In an analogous manner, compounds IV, VII, IX, XII, and XVI showed activity against serotonin or amphetamine. This might be due to the fact that electron density around the carbonyl-carbon is affected by the presence of *p*-chloro and 3-methoxy groups. These groups, being polar, also affect the partition coefficient of the molecule. Compounds II and IV showed the maximum antiserotonin activity, whereas compounds I and XIV exhibited the maximum antiamphetamine activity.

From these observations, it may be concluded that replacing the dimethylaminopropyl side chain of 10,11-dihydrodibenzo[*a*,*d*]cycloheptadiene with oximino-esters leads to potent ataractic agents. Another observation from this study indicates that conjugation of the benzene rings is not essential for activity. The 1-phenyl-1,2-propanedione-2-oxime esters showed that the electron density of the 1-carbonyloxygen might be helping the molecule in binding more effectively to the receptor site.

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