Aporphines. 34. (-)-2,10,11-Trihydroxy-*N*-*n*-propylnoraporphine, a Novel Dopaminergic Aporphine Alkaloid with Anticonvulsant Activity

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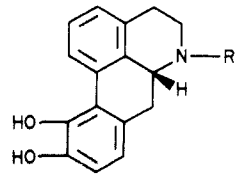
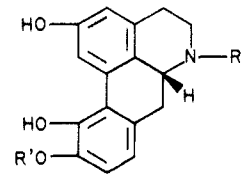
(-)-2,10,11-Trihydroxy-*N*-*n*-propylnoraporphine (TNPA, **2c**) has been synthesized from thebaine (**3a**), via northebaine (**3b**), normorphothebaine (**2a**), and alkylation to the *N*-propyl derivative **2b**. O-Demethylation gave the desired product **2c**. Compound **2c** showed activity comparable to its 10,11-dihydroxy counterpart (NPA, **1b**) on the stimulation of dopamine-sensitive adenylate cyclase in carp retinal homogenates. The evaluation of **2c** on audiogenic seizures in mice, in the protection against paroxysimal EEG and myoclonic response to photic stimulation in the baboon, revealed a similar pharmacological profile in comparison to NPA and apomorphine, with TNPA showing a prolonged duration of action in abolishing myoclonic response to photic stimulation in the baboon.

The clinical utilization of apomorphine (APO, **1a**) in the



1a (APO), R = CH_3
b (NPA), R = *n*-propyl



2a (normorphothebaine), R = H; R' = CH_3
b, R' = CH_3; R = *n*-propyl
c (TNPA), R' = H; R = *n*-propyl

treatment of various forms of epilepsy dates back to 1877.[1] More recently, Lal and his co-workers[2-4] observed that APO antagonized extreme photosensitivity in a patient with Kuf's disease and found that APO·HCl (1.24-1.5 mg sc) in 9 of 11 patients with primary corticoreticular epilepsy, in whom generalized epileptic discharges were regularly induced by photic stimulation, induced a transient total blockade in the photosensitive response commencing 15 ± 1.8 min after injection and lasting 45 ± 5 min. The blockade was independent of side effects of APO and was not associated with EEG or clinical evidence of drowsiness.

It is recognized that dopamine (DA) exerts an inhibitory effect on neocortical neurons in various species, and in the cat photic stimulation reduces the release of endogenous DA in the visual cortex.[5] APO and other dopamine agonists protect against paroxysmal EEG and myoclonic response to photic stimulation in the Senegalese baboon, *Papio papio*.[6] Thus, it seems reasonable to suggest that the beneficial effects of DA and DA agonists in the pathophysiology of photically induced seizures in man are

Table I. Dopamine Agonist and Audiogenic Seizures in DBA/2 Mice

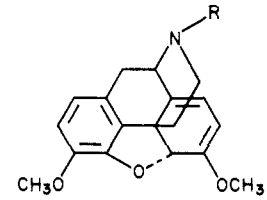
drug	interval, min	clonic ED_{50}, mg/kg	ref
(-)-APO (**1a**)	20	0.7	9
(-)-NPA (**1b**)	30	0.075	10
(-)-TNPA (**2c**)	30	0.72	
bromocryptine	60	5.0	11

Table II. Abolition of Myoclonic Responses to Photic Stimulation in the Baboon, *Papio papio*

drug	min dose, mg/kg	duration of protection, min	ref
(-)-APO	0.5	30-45	6
(-)-NPA	0.2	180	10
(-)-TNPA	0.5	180-300	

exerted by stimulation of DA receptors. In this paper, we report the synthesis of (-)-2,10,11-trihydroxy-*N*-*n*-propylnoraporphine hydrobromide (TNPA·HBr, **2c**), an analogue of APO and NPA (**1b**), and its preliminary pharmacological evaluation on audiogenic seizures in mice, in the protection against paroxysmal EEG and myoclonic responses to photic stimulation in the baboon, and on DA-sensitive adenylate cyclase in homogenates of carp retina.

N-Demethylation of thebaine (**3a**) was carried out by



3a (thebaine), R = CH_3
b (northebaine), R = H

the procedure of Pohland and Sullivan[7] and directly subjected to acid rearrangement to give normorphothebaine (**2a**) as recently described.[8] Realkylation with propyl

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Table III. Effect of DA, (−)-NPA, and (−)-TNPA on Adenylate Cyclase Activity in Homogenates of Carp Retina

drug	% max response elicited by 100 μM DA[a]
100 μM DA	100
100 μM (−)-NPA	58.9 ± 1.8
10 μM (−)-NPA	69.7 ± 2.1
100 μM (−)-TNPA	59.4 ± 2.3
10 μM (−)-TNPA	43.4 ± 3.3

[a] Each value is taken from a single experiment involving four to six determinations (mean ± SEM). Results are expressed as percent maximum response elicited by 100 μM DA.

iodide was carried out in acetonitrile to yield the *N*-propyl-substituted normorphothebaine (**2b**). Treatment of **2b** with 48% HBr at elevated temperatures yielded the desired compound **2c**.

DBA/2 mice, 18–28 g, show a fixed sequence of seizure phenomena in response to a loud sound. DA agonists prevent the later stages of this reponse (Table I). When administered ip in the mouse, TNPA had a prolonged sedative action. In terms of ED_{50} for the clonic phase of the seizure response, **2c** is equipotent with apomorphine (tested 30 min after drug administration).

DA agonists protect against paroxysmal EEG and myoclonic responses to photic stimulation in *Papio papio* (Table II). In this model of epilepsy, seizure responses are potentially modified by drugs acting on serotoninergic transmission.[12] TNPA, 0.02 mg/kg iv, produced a mild sedative effect but did not modify myoclonic responses to photic stimulation. However, complete protection was seen for 3–7 h after TNPA, 0.5 and 2.5 mg/kg, was given intravenously. These doses were also followed by pupil dilation, yawning, slowing of EEG background rhythms, and, at the highest dose, by excess salivation and piloerection.

The presence of substantial amounts of a highly specific dopamine-sensitive adenylate cyclase in carp (*Cyprinus carpio*) retinal homogenates which possesses a pharmacological profile similar to the dopamine-sensitive adenylate cyclase found in other areas of the brain[13] make this a useful model in which to evaluate the activity of dopamine agonists. When tested in this system using methods previously described,[13] TNPA produced a significant stimulation of adenylate cyclase activity in comparison with (−)-NPA and DA (Table III).

These findings support the suggestion that DA plays an important role in the pathophysiology of photically induced seizures in man and animals. The observation that dopamine agonists block the reflex induction of a variety of seizure phenomena further suggests the potential utility of a DA agonist such as TNPA in therapy. Such a DA agonist in combination with an antagonist that blocks nausea and autonomic effects (such as domperidone) might be useful in some forms of myoclonus and photosensitive epilepsy. The activity of these and related trihydroxylated aporphines evaluated against the high-affinity (nM) binding of [^{3}H]APO and [^{3}H]spiroperidol to subsynaptosomal membrane preparations of bovine caudate nucleus tissue compared with both mono- and dihydroxylated aporphines will be reported in a forthcoming publication.[14] These results add further support to the present findings that **2c** is a potent dopamine agonist.

Experimental Section

General Methods. All melting points were taken on a Thomas-Hoover apparatus and are uncorrected. Analyses were performed by Galbraith Laboratories, Knoxville, TN. Thin-layer chromatography (TLC) was performed on precoated silica gel 13179, polyethylene terephthalate foils (Eastman Kodak, Rochester, NY). Column chromatography was performed on silica gel (Baker, 5-3405, 60–200 mesh). The IR spectra were obtained with a Parkin-Elmer Model 700 or Beckman IR10 spectrophotometer. The NMR spectra were measured in $CDCl_3$ or CD_3S–OCD_3 or CD_3OD on a Varian T-60 spectrometer, and chemical shifts are reported in parts per million (δ) downfield from $(CH_3)_4Si$ as internal standard. Mass spectra were determined on a 12-90-G nuclide mass spectrometer. Optical rotations were obtained on a Perkin-Elmer polarimeter (Model 141).

***N*-*n*-Propylnormorphothebaine (2b).** A mixture of normorphothebaine hydrochloride[8] (5.1 g, 0.016 mol), $NaHCO_3$ (5.0 g, 0.06 mol), and *n*-propyl iodide (4.8 g, 0.028 mol) in 130 mL of acetonitrile was heated at 100 °C under N_2 for 16 h. The reaction mixture was cooled and filtered, and the filtrate was evaporated to a residue. The residue was treated with 100 mL of chloroform and filtered, and the filtrate was concentrated to an approximately 5 mL solution, which was then chromatographed on silica gel (1:30) packed and eluted with 5% $CH_3OH/CHCl_3$ to give the desired product. The HCl salt (3.0 g, 51%) was prepared by adding excess ethereal HCl to the eluent containing pure **2b** to form a white precipitate, which was then collected by filtration: mp 214–216 °C dec; NMR and mass spectra were consistent with the assigned structure; UV (EtOH) λ_{max} 268 nm (log ϵ 4.14), 278 (4.14), 305 (3.89); $[\alpha]^{25}_{546}$ −60°. Anal. ($C_{20}H_{23}NO_3 \cdot HCl \cdot 1.5H_2O$) C, H, N.

***N*-*n*-Propyl-2,10,11-trihydroxynoraporphine (2c).** A mixture of **2b** (0.50 g, 1.28 mmol) in 15 mL of 48% HBr was heated at 130 °C for 3 h. The reaction mixture was cooled and evaporated to a dry residue in vacuo. The residue was recrystallized from CH_3OH–Et_2O to give an off-white solid (0.35 g, 70%): mp 203–206 °C dec; NMR and mass spectra were consistent with the assigned structure; UV (EtOH) λ_{max} 270 nm (log ϵ 4.13), 280 (4.15), 303 (3.86); $[\alpha]^{25}_{546}$ −62°. Anal. ($C_{19}H_{21}NO_3 \cdot HBr \cdot 2H_2O$) C, H, N.

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