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Leonurine, an improved synthesis[1]

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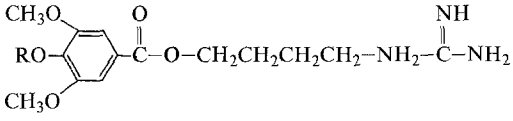
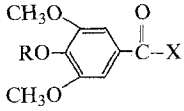
Summary. Leonurine (**1**) is the uterotonic principle of *Leonurus artemisia.* We have developed a simple, high-yield synthetic procedure of **1** that is adaptable to large scale preparation. The synthesis involves the condensation of syringic acid and 4-guanidino-1-butanol hydrochloride in the presence of DDC using 1:1 HMPT-ether as solvent. The synthetic leonurine showed uterotonic activity in vivo and in vitro.

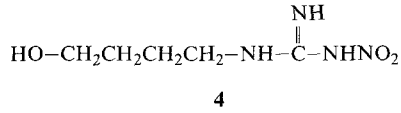
Leonurine (**1**) had been isolated from the leaves of *Leonurus sibiricus* L. and its structure established[2]. We have recently isolated leonurine from *L. artemisia* grown in Hong Kong and demonstrated the uterotonic activity in vivo and in vitro[3,4].



1

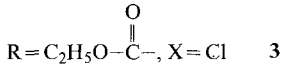
The reported synthesis[2] of **1** starting from syringic acid (**2**) involves the condensation of carboethoxy syringic acid chloride (**3**) with 4-(N-nitroguanidino)-1-butanol (**4**) in pyridine.





4

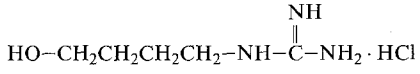
R = H, X = OH **2**



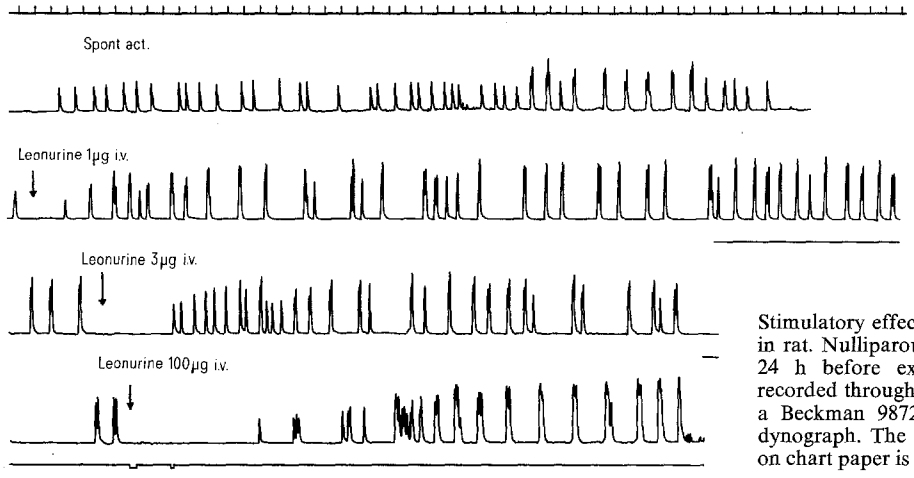
3

The function of the carboethoxy group in **3** and the nitro group in **4** is to protect the phenolic hydroxy group and the guanidino group during condensation. The introduction and subsequent removal of these protecting groups, together with the necessity to convert the carboxylic acid to its acid chloride prior to condensation, make the synthesis rather lengthy and inefficient. Furthermore, we have repeated the synthesis several times and obtained **1** in very low yield. The main difficulty was the removal of the carboethoxy protecting group with base which caused the guanidino group to polymerize, and the removal of the nitro group by catalytic reduction which failed to occur. Attempt to improve the reduction step by employing various conditions[5,6] was unsuccessful.

Recently we had the need to synthesize a large amount of **1**. Due to the difficulty involved in the synthesis according to literature, we decided to investigate the feasability of preparing **1** by a 2-step procedure involving first conversion of 4-amino-butanol to 4-guanidino-1-butanol hydrochloride (**5**), followed by direct condensation of **5** with syringic acid (**2**) in the presence of dicyclohexylcarbodiimide (DCC).



5



Stimulatory effect of leonurine on intrauterine pressure in rat. Nulliparous rat was primed with 10 µg estradiol 24 h before experiment. Intrauterine pressure was recorded through a Statham P23BB transducer linked to a Beckman 9872 pressure coupler in a model 511A dynograph. The timer marks at 1-min intervals. 1 mm on chart paper is equal to 1 mm Hg.

DCC has been known to promote ester condensation[7] conducted in the following solvents: ether, dioxan, THF, DME, pyridine, chloroform and acetonitrile. However, as expected, none of these nonpolar solvents dissolves the ionic hydrochloride salt **5**. Other aprotic polar solvents were employed. We found that condensation of **2** and **5** in DMF or 1:1 DMF-acetonitrile afforded a complex product mixture from which was isolated small amount of **1** (7%). On the other hand, if condensation of **2** with **5** in the presence of DCC was conducted in hexamethylphosphoric triamide (HMPT) or 1:1 HMPT-ethyl ether at room temperature for 72 h, **1** was obtained in good yield (80%). Compound **1** thus obtained was identical in all respects (TCL, IR, NMR, MS) to the natural leonurine hydrochloride isolated from *L. artemisia*. In addition to the efficiency of the method, this procedure is adaptable to large scale preparation. Although DCC has been used for the preparation of ester, however, to our knowledge, this reagent has not been used previously for the direct preparation of guanidino ester. Thus the synthesis of **1** from **2** and **5** represents an efficient direct method for the preparation of other guanidino ester.

The synthetic leonurine was found to stimulate uterine contraction when tested with isometric contraction of rat uterus human mymetrium in vitro. At 0.1 µg/ml of physiologic medium, leonurine can change an irregular contraction pattern of small amplitude into regular contraction cycles of large amplitude. This stimulatory effect was also observed under in vivo conditions[8]. At a dose of 1–10 µg given i.v., intrauterine pressure in rat was raised from basal level to regular contraction cycles of 15–20 mm Hg.

1 Acknowledgment. This work was partly supported by World Health Organization, Geneva, Switzerland.
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ZNS-aktive Phenylpropylamine von *Catha edulis* FORSK. (Celastraceae) kenyanischer Herkunft

CNS-active phenylpropylamines of *Catha edulis* FORSK. (Celastraceae) of Kenyan origin

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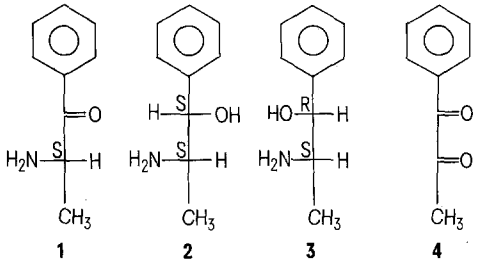
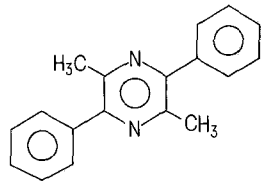
Summary. The phenylpropylamine fraction of *Catha edulis* FORSK. grown in Kenya has been investigated. The major components have been found to be (S)-(−)-α-aminopropiophenone (**1**), (+)-norpseudoephedrine (**2**) and (−)-norephedrine (**3**). Quantitative ratios of **1**, **2**, **3** in tissues of different age are discussed.

Infolge ihrer Verwendung als stimulierende Genussdroge war *Catha edulis* FORSK. (Khat, Miraa) mehrfach Gegenstand phytochemischer Untersuchungen[1-5], deren zum Teil widersprüchlichen Ergebnisse bis anhin nicht befriedigen konnten. Zudem stellte sich aus biogenetischen Überlegungen die Frage nach dem Vorhandensein weiterer Komponenten, insbesondere der N-methylierten Phenylpropylamine, wie sie in Ephedra-Arten anzutreffen sind, nachdem bis vor kurzem einzig das als Cathin bezeichnete (+)-Norpseudoephedrin als ZNS-stimulierendes Prinzip zweifelsfrei identifiziert worden war[6]. Konkrete Hinweise auf eine weitere ZNS-aktive Substanz ergaben sich aus pharmakologischen Untersuchungen mit aus Khat extrahierten Stoffen an Mäusen[7], was durch eine Mitteilung[8] aus dem Suchtlabor der Vereinten Nationen über die Isolierung des Cathinons (**1**) als dem (−)-α-Aminopropiophenon bestätigt wurde.

Um möglichst vollständige Angaben über die Phenylpropylamin-Fraktion zu erhalten, untersuchten wir frisches und getrocknetes Pflanzenmaterial aus Catha-Kulturen im Hinterland von Meru (Kenya), und zwar vor allem die zu Genusszwecken bestimmten Jungtriebe und Blätter verschiedenen Alters, d.h. Blätter in unterschiedlichen Entwicklungsstadien. Die Gesamt-Phenylpropylamine wurden nach verschiedenen Extraktionsmethoden[9] vorzugsweise in Form ihrer Oxalate oder N-acetylierten Derivate isoliert und anschliessend schichtchromatographisch in die Einzelkomponenten aufgetrennt. Die spektroskopischen Daten (MS, ^{1}H-NMR, IR, UV, CD) bestätigen auch für unser Pflanzenmaterial das Vorliegen des Cathinons, dessen Identität in Auswertung des CD-Spektrums[10] unter Verwendung einer Quadranten-Sektoren-Regel[11,12] mit dem synthetischen (S-)-(−)-α-Aminopropiophenon (**1**) bewiesen werden konnte. Die Bestimmung der absoluten



1 **2** **3** **4**



5

1 (S)-(−)-α-Aminopropiophenon
2 (+)-Norpseudoephedrin
3 (−)-Norephedrin
4 1-Phenyl-1,2-propandion
5 3,6-Dimethyl-2,5-diphenylpyrazin