研究简报

用^2H－标记物和GC－MS分离鉴定联苯双酯在大鼠尿中的一个代谢产物

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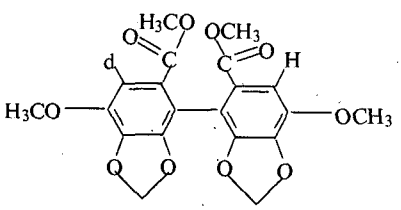
联苯双酯(BDD)是人工合成的五味子丙素类似物，其化学结构为4,4′－二甲氧基－5,6,5′,6′－二次甲二氧基－2.2′－二甲氧羰基联苯，已用于迁、慢性肝炎的治疗。临床证明，该药降血清谷丙转氨酶的作用很强。为阐明其在体内的转化过程，并进一步研究其构效关系，我所曾用放射性同位素结合薄层层析对联苯双酯的代谢途径进行过研究，并分离鉴定了其代谢产物[1,2]，发现联苯双酯可被肝脏迅速代谢，代谢途径主要为脱甲基，部分进而与葡萄糖醛酸结合。

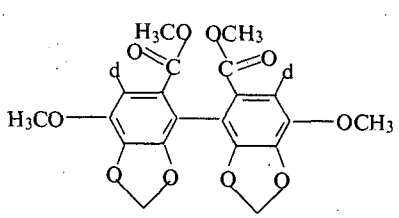
本文用稳定性同位素氘标记的联苯双酯结合气相色谱—质谱(GC—MS)联用技术，分离鉴定出了一个代谢产物，方法简便快捷。此结果证实了以前的发现。

实验部分

为了找到并研究联苯双酯的代谢物，我们使用了氘标联苯双酯3－d－BDD和3,3′－2d－BDD.



3－d－BDD



3,3′－2d－BDD

取体重150～250 g雄性Wistar大鼠4只分放两个代谢笼内，给药前禁食12 h，自由饮水。将未标记的联苯双酯和氘标记的联苯双酯(其中单氘代与双氘代物的比例约为1:1.3)按一定比例混合，用吐温－80制成悬液。按150 mg/kg灌胃给药，然后收集24 h尿。鼠尿用微孔滤膜过滤后，用二氯甲烷提取3次，每次5 ml。将提取液混合后，在35 ℃下减压蒸

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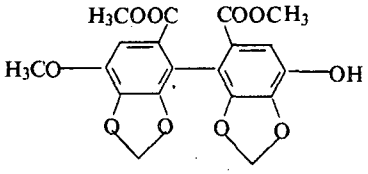
干，将残渣用氯仿重新溶解。供 GC－MS 分析。

使用的仪器是 HP5790 气相色谱和 HP5970A 质谱检测器。色谱柱前压 0.4 kg/cm²；OV－1 石英毛细管柱，柱长 14 m。离子源温度 200 ℃；轰击能量 70 eV。载气为高纯氦气。进样后质谱检测器接收并记录总离子流图。

经 GC－MS 分析后，得到服药后鼠尿提取物的总离子流图，见图 1a．观察各峰的质谱，发现 12.2 min 处的一个小峰为原型药。此原型药极性稍大，12.9 min 处有一个较大的峰，它的质谱图(图 1 b．)中有几组“三姊妹”峰，m/z：404，405，406；373，374，375；345，346，347；330，331，332 等等。这几组中“三姊妹”的质荷比的相互关系均为 M，M＋1，M＋2，与联苯双酯和其一氘及二氘代物的质量关系相对应，认为与原型药的母体结构有关，是一个代谢产物。其中基峰和主要碎片峰与联苯双酯的基峰和主要碎片峰顺序相同，但质荷比均少 14 个单位（－CH_2）因此判定这个物质为去甲基联苯双酯。这一结果证实了我所以前的发现，即联苯双酯代谢产物之一为去甲基联苯双酯。



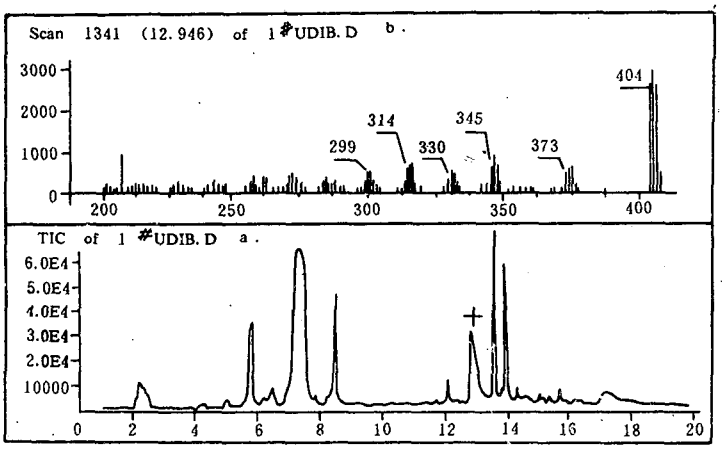


Fig 1．a. The total ion chromatogram of an extract of the urine of a rat given a mixture of deuterium labeled BDD and non－labeled BDD．　b．Mass spectrum of the peak at 12.9 min．

关键词 联苯双酯；4,4′－二甲氧基－5,6,5′,6′－二次甲氧基－2,2′－二甲氧羰基联苯；氘标记化合物；稳定性同位素；气相色谱—质谱

参 考 文 献

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2．王晓良，等．联苯双酯代谢产物的分离和鉴定．同上　1984；**19**：12．

USE OF ^{2}H-LABELED COMPOUND AND GC-MS IN THE ISOLATION AND IDENTIFICATION OF A METABOLITE OF BIPHENYLDIMETHYL-DICARBOXYLATE IN RAT URINE

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ABSTRACT Dimethyl-4, 4′-dimethoxy-5, 6, 5′, 6′-dimethylenedioxy-biphenyl-2, 2′-dicarboxylate (biphenyldimethyldicarboxylate; BDD), a synthetic compound, has been used in the treatment of chronic hepatitis with good results in reducing s-GPT. Previous work in our laboratory studied its metabolites using ^{3}H-labeled compound in combination with TLC and found that its main methabolic pathway is demethylation followed by conjugation with glucuronic acid. This paper reports the isolation and identification of a metabolite of BDD from rat urine using ^{2}H-labeled compound and GC-MS. Rats fasted for 12 h were intragastrically given a mixture of ^{2}H-labeled (consisting of monodeutero- and dideutero-BDD in the ratio about 1:1.3) and non-labeled BDD 150 mg/kg and placed in metabolism cages for urine collection. The 24 h urine was filtered and extracted three times each with 5 ml of methylenedichloride. The extracts were pooled and evaporated to dryness under reduced pressure at 35 ℃. The residue was redissolved in chloroform and subjected to GC-MS analysis. The mass spectrum (m/z: 404, 405, 406; 373, 374, 375; 345, 346, 347; 330, 331, 332; etc) indicates that the molecular ionic and fragment peaks of the metabolite all have 14 amu less than those of BDD. This means that the metabolite isolated is mono-O-demethylated BDD. The result confirmed our findings reported previously.

Key words Biphenyldimethyldicarboxylate; Dimethyl-4,4′-dimethoxy-5,6,5′, 6′-dimethylenedioxybiphenyl-2,2′-dicarboxylate; Deuterium labeled compound; Stable isotope; Gas chromatography-mass spectrometry