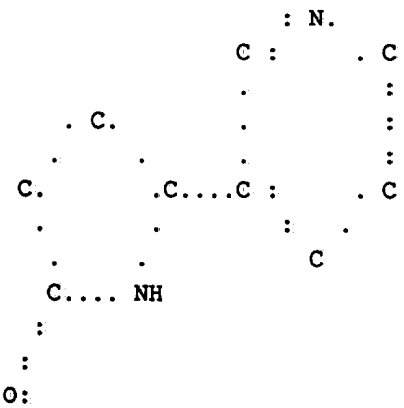
RN 5980-06-3
CN 2-Pyrrolidinone, 5-(3-pyridinyl)-, (S)- (9CI) (CA INDEX NAME)
CN Norcotinine
CN (-)-Demethylcotinine
CN Cotinine, demethyl- (7CI, 8CI)
CN Demethylcotinine
CN S-(-)-Norcotinine
MF C9 H10 N2 O
LC BEILSTEIN
STE 1:S



REFERENCES IN FILE CAOLD (PRIOR TO 1967)
24 REFERENCES IN FILE CA (1967 TO DATE)

BRN 131863 Beilstein
MF C9 H10 N2 O
SY 3-Norcotinin
FW 162.19
RN ***5980-06-3*** ; 17114-40-8; 17708-87-1; 120203-40-9

Preparation:
Reference(s):
1. Glenn, Edwards, J.Org.Chem., 43, <1978>, 2860,2865,2868, CODEN: JOCEAH

BRN 82570 Beilstein
MF C9 H10 N2 O
CN (+-)-5-<3>pyridyl-pyrrolidin-2-one
(+-)-5-<3>Pyridyl-pyrrolidin-2-on
FW 162.19
NTE and mirror-image.
RN ***5980-06-3*** ; 17114-40-8; 17708-87-1; 120203-40-9

Preparation:
Start: 4-oxo-4-<3>pyridyl-butyric acid, NH3
Reag: Raney-nickel, ethanol
Temp: 130.0 Cel
Press: 5.8840632E+04 Torr
Detail: Hydration
Reference(s):
1. McKennis et al., J.Amer.Chem.Soc. 81 <1959> 3951, 3953, CODEN: JACSAT
Note(s):
2. Handbook Data

Preparation:
Start: 4-hydroxyimino-4-<3>pyridyl-butyric acid
Reag: zinc-powder, acetic acid, ethanol
Reference(s):
1. McKennis et al., J.Amer.Chem.Soc. 80 <1958> 1634, CODEN: JACSAT
Note(s):
2. Handbook Data

Preparation:
Start: (+-)-4-amino-4-<3>pyridyl-butyric acid ethyl ester
Temp: 200.0 Cel
Reference(s):
1. Zymalkowski, Trenktrog, Arch.Pharm.(Weinheim Ger.) 292 <1959> 9, 13, CODEN: ARPMAS
Note(s):
2. Handbook Data

BRN 82569 Beilstein
MF C9 H10 N2 O
CN (R)-5-<3>pyridyl-pyrrolidin-2-one
(R)-5-<3>Pyridyl-pyrrolidin-2-on
FW 162.19
RN ***5980-06-3*** ; 17114-40-8; 17708-87-1; 120203-40-9

Preparation:
Start: (+-)-5-<3>pyridyl-pyrrolidin-2-one
Reag: (1S)-2-oxo-bornane-10-sulfonic acid
Reference(s):
1. McKennis et al., J.Amer.Chem.Soc. 81 <1959> 3951, 3954, CODEN: JACSAT
Note(s):
2. Handbook Data

BRN 82568 Beilstein
MF C9 H10 N2 O
CN (S)-5-<3>pyridyl-pyrrolidin-2-one
(S)-5-<3>Pyridyl-pyrrolidin-2-on
FW 162.19
RN ***5980-06-3*** ; 17114-40-8; 17708-87-1; 120203-40-9

Preparation:
Start: (+-)-5-<3>pyridyl-pyrrolidin-2-one
Reag: (1S)-2-oxo-bornane-10-sulfonic acid
Reference(s):
1. McKennis et al., J.Amer.Chem.Soc. 81 <1959> 3951, 3953, CODEN: JACSAT
Note(s):
2. Handbook Data

L3 ANSWER 1 OF 24
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AN CA112(5):31756m
AU Smith, C. L.; O'Doherty, S.; Cooke, M.; Roberts, D. J.
TI Determination of nicotine metabolites by HPLC after complexation with diethylthiobarbituric acid
SO Anal. Proc. (London), 26(10), 348-51
AB The diethylthiobarbituric acid extn. method followed by HPLC has proved to be a useful method for the detection of the various nicotine metabolites in the urine of cigaret smokers. trans-3-Hydroxycotinine now appears to be the major metabolite of nicotine, replacing cotinine in importance and with this method up to 50% of the input nicotine can be traced as nicotine, cotinine, and 3-hydroxycotinine. More complicated procedures, such as radiometric HPLC-mass spectrometry are able to trace up to 85% of the metabolites and it is hoped that this colorimetric method will enable further studies on the complex metab. of nicotine to take place, and other metabolites to be identified and quantitated.
IT 54-11-5, Nicotine 54-11-5D, Nicotine, metabolites 486-56-6, Cotinine ***5980-06-3*** , Demethylcotinine 34834-67-8, trans-3-Hydroxycotinine 37096-14-3
(detection of, in urine of human smokers by HPLC with colorimetric detection)

L3 ANSWER 2 OF 24
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AN CA110(11):90460s
AU Kyerematen, G. A.; Owens, G. F.; Chattopadhyay, B.; DeBethizy, J. D.; Vesell, E. S.
TI Sexual dimorphism of nicotine metabolism and distribution in the rat. Studies in vivo and in vitro
SO Drug Metab. Dispos., 16(6), 823-8
AB Interpretation of sex differences in nicotine metab. and disposition in rats required studies both in vivo and in vitro to provide both metabolic and pharmacokinetic data. In each of four rat strains studied in vitro, males metabolized nicotine faster than did females. In Sprague-Dawley rats, studies of nicotine kinetics after a single i.v. dose of [14C]nicotine revealed a larger nicotine vol. of distribution in females than in males. A prolonged plasma nicotine half-life in females balanced the larger vol. of distribution, so that no sex difference appeared in plasma clearance of nicotine. Nevertheless, sex differences in nicotine metab. are indicated inasmuch as (1) females had lower plasma cotinine concns. than did males; (2) urinary recoveries of nicotine were higher in female than in male rats; (3) total urinary output of nicotine metabolites was higher in male than female rats, consistent with the

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enhanced N- and C-oxidn. of nicotine by male rats obsd. in vitro. In female rats, the reduced rate of nicotine metab., as well as a larger vol. of distribution of nicotine, explains in part the reported increased lethality of female compared with male rats.

IT 494-97-3, Nornicotine 501-81-5, 3-Pyridylacetic acid 713-05-3 2820-55-5, Nicotine-N-oxide 4192-31-8, .gamma.-(3-Pyridyl)-.gamma.-oxobutyric acid ***5980-06-3*** , Demethylcotinine 15569-99-0, .gamma.-(3-Pyridyl)-.gamma.-methylaminobutyric acid 34834-67-8, 3-Hydroxycotinine 36508-80-2, Cotinine-N-oxide 118995-81-6 118995-82-7
(as nicotine metabolite, in urine, sex in relation to)

L3 ANSWER 3 OF 24

AN CA108(21):181970h

AU Domelloef, Lennart; Andersson, Magnus; Tjaelve, Hans; Veals, Susan; Trushin, Neil; Hecht, Stephen S.

TI Distribution and metabolism of N'-nitrosonornicotine in the miniature pig

SO Carcinogenesis (London), 8(11), 1741-7

AB The distribution and metab. of [5-3H]N'-nitrosonornicotine ([5-3H]NNN) (I) was studied in 3 18-day-old miniature pigs. [5-3H]NNN was administered by intracardiac administration into the right ventricle of the heart to mimic uptake by the lung. Whole body autoradiograms taken 15-220 min after treatment showed high levels of radioactivity in the mandibular and parotid salivary glands, Harder's gland, lacrimal glands, glands of the snout and respiratory part of the nasal cavity, and the melanin of the eyes and skin. Bound radioactivity was most abundant in the nasal mucosa and liver. Anal. of tissues by HPLC showed the presence of high levels of [5-3H]NNN in the mandibular glands and Harder's gland. Levels of [5-3H]NNN and its metabolites were detd. in arterial and venous serum, 0.5-220 min after injection. The disappearance of [5-3H]NNN from serum was biphasic. 4-Oxo-4-(3-pyridyl)butyric acid, a metabolite of [5-3H]NNN resulting from 2'-hydroxylation, which is a suspected activation pathway, was detected 0.5 min after injection and appeared to reach a steady state 2-220 min after injection. 4-Hydroxy-4-(3-pyridyl)butyric acid, from 5'-hydroxylation of [5-3H]NNN, and norcotinine, from denitrosation, were also rapidly formed. These expts. are the 1st in which the appearance of NNN metabolites in blood was measured. The ratio of 2'-hydroxylation to 5'-hydroxylation varied from 0.27 to 0.60 in arterial serum and from 0.33 to 0.49 in venous serum in the period from 2-220 min. [5-3H]NNN accumulated in the stomach contents such that its levels were greater than those in arterial or venous serum, 60 min after injection. The results of this study demonstrate that the miniature pig is a useful model for the investigation of nitrosamine metab.

and indicate some similarities and differences in metab. and distribution compared with the rat.

IT 4192-31-8, 4-Oxo-4-(3-pyridyl)butyric acid ***5980-06-3*** , Norcotinine 15569-97-8, 4-Hydroxy-4-(3-pyridyl)butyric acid
(as nitrosonornicotine metabolite, in miniature swine)

L3 ANSWER 4 OF 24

AN CA108(17):145265y
AU Kyerematen, G. A.; Taylor, L. H.; DeBethizy, J. D.; Vesell, E. S.
TI Pharmacokinetics of nicotine and 12 metabolites in the rat. Application of a new radiometric high performance liquid chromatography assay
SO Drug Metab. Dispos., 16(1), 125-9
AB A new radiometric assay for nicotine (I) and 12 of its metabolites disclosed that plasma I and cotinine t1/2.beta. were independent of dose after single intraarterial I doses of 0.1, 0.5, or 1.0 mg/kg. At high doses, I area under the curve and clearance tended to exhibit a small degreed of dose dependency. The longest lived metabolites, cotinine N-oxide and a previously unidentified metabolite now revealed to be allohydroxydemethylcotinine, persisted for 96 h after I injection, whereas cotinine was detected for only 48 h. Cotinine, formerly considered the longest lived I metabolite, serves widely as the most sensitive indicator of prior exposure to small concns. of I. The present studies disclose new, longer lasting metabolites that may perform this function more sensitively, at least in the rat. At the 3 doses of I administered, plasma I half-life ranged from 0.9 to 1.1 h, total body clearance of I ranged from 2.9 to 3.9 L.cntdot.h-1.cntdot.kg-1; and apparent vol. of distribution of I from 4.7 to 5.7 L.cntdot.kg-1. Also at these 3 doses, mean half-lives of urinary excretion of cotinine, cotinine N-oxide, and allohydroxydemethylcotinine ranged from 4.8 to 5.3 h, from 7.9 to 8.2 h, and from 9.9 to 11.0 h, resp.
IT 54-11-5, Nicotine 54-11-5D, Nicotine, metabolites 486-56-6, Cotinine 491-26-9, Nicotine-1'-N-oxide 494-97-3, Nornicotine 501-81-5, 3-Pyridylacetic acid 713-05-3 4192-31-8 ***5980-06-3*** , Demethylcotinine 15569-99-0 34834-67-8, 3-Hydroxycotinine 36508-80-2, Cotinine-N-oxide 45791-94-4
(pharmacokinetics of)

L3 ANSWER 5 OF 24

AN CA107(21):192367x
AU Kyerematen, G. A.; Taylor, L. H.; deBethizy, J. D.; Vesell, E. S.
TI Radiometric high-performance liquid chromatographic assay for nicotine and twelve of its metabolites
SO J. Chromatogr., 419, 191-203

AB A sensitive, reproducible radiometric HPLC assay was developed to measure concns. of nicotine (I) and 12 of its metabolites in biol. fluids. Following the administration of 0.1 mg I/kg (labeled in [2-14C]pyrrolidine) to rats, the assay was used in a pharmacokinetic investigation. Radioactivity due to I and cotinine was detected in substantial amts. in plasma samples. I disappearance was biexponential, with an elimination half-life of 1.0 h. Cotinine appeared as the major metabolite in plasma and had elimination half-life 5.2 h. In urine, nicotine-1'-N-oxide was the major metabolite of I.

IT 54-11-5, Nicotine 54-11-5D, Nicotine, metabolites 486-56-6, Cotinine 491-26-9, Nicotine-1'-N-oxide 494-97-3, Nornicotine 501-81-5, 3-Pyridylacetic acid 713-05-3 4192-31-8, .gamma.-(3-Pyridyl)-.gamma.-oxobutyric acid ***5980-06-3*** , Demethylcotinine 10516-09-3, 6-Hydroxynicotine 15569-99-0, .gamma.-(3-Pyridyl)-.gamma.-methylaminobutyric acid 34834-67-8, 3-Hydroxycotinine 85805-66-9
(detn. of, in biol. fluids by radiometric-HPLC assay)

L3 ANSWER 6 OF 24

AN CA107(11):94922e
AU Bjercke, Robert J.; Langone, John J.
TI Monoclonal anti-idiotypic antibodies that recognize the binding site for nicotine on rat brain receptor
SO Biochem. Biophys. Res. Commun., 145(2), 847-53
AB Anti-idiotypic monoclonal antibodies have been prepd. that represent the internal image of nicotine and are specific for the nicotine binding site on rat brain receptor. Specificity of these antibodies for the combining site on anti-nicotine was demonstrated by their ability to inhibit binding of monoclonal anti-nicotine to immobilized nicotine-polylysine. Furthermore, purified rat brain nicotine receptor but not acetylcholine receptor from fish elec. organ effectively competed with anti-nicotine for immobilized nicotine and for immobilized anti-idiotype. Only 9 pmoles of naturally occurring (-)-nicotine inhibited idiotype-anti-idiotype binding by 50% whereas 11-fold more (+)-nicotine was required. Acetylcholine, several cholinergic agonists and antagonists, nicotine metabolites, and other structurally related compds. were poor inhibitors.

IT 51-55-8, Atropine, biological studies 51-84-3, Acetylcholine, biological studies 57-94-3 59-99-4, Neostigmine 60-26-4, Hexamethonium 60-40-2 156-74-1, Decamethonium 462-58-8, Carbamylcholine 485-35-8, Cytisine 486-56-6, (-)-Cotinine 491-26-9, Nicotine N'-oxide 494-52-0, Anabasine 494-97-3, (-)-Nornicotine 532-12-7, Myosmine 4192-31-8, .gamma.-(3-Pyridyl)-.gamma.-oxobutyric acid 5979-92-0 ***5980-06-3*** 11032-79-4, .alpha.-Bungarotoxin 36508-80-2

(anti-nicotinic and anti-idiotypic antibodies reactivity with)

L3 ANSWER 7 OF 24

AN CA104(3):16366a
AU Castonguay, Andre; Tjaelve, Hans; Trushin, Neil; D'Argy, Roland; Sperber, Goeran
TI Metabolism and tissue distribution of tobacco-specific N-nitrosamines in the marmoset monkey (Callithrix jacchus)
SO Carcinogenesis (London), 6(11), 1543-50
AB Three male marmoset monkeys were injected i.v. with 2'-14C-labeled N-nitrosonornicotine (I) [16543-55-8] (20.3 .mu.mol/kg) or carbonyl-14C-labeled 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (II) [64091-91-4] (18.8 or 420 .mu.mol/kg). They were sacrificed 4 h later. Tissue distribution was studied in 2 monkeys by whole-body autoradiog. and computer-assisted densitometric anal. of the autoradiograms. The autoradiograms showed a high level of radioactivity in the liver, nasal mucosa, kidneys, melanin of the eyes, hair-follicles of the skin, and in the ceruminous ear glands of the monkeys. Total level of radioactivity was 5.7 times higher in the liver of the [carbonyl-14C]II-injected monkey than in the [2'-14C]I-injected monkey. Washing the sections with Cl3CO2H and org. solvents selectively removed free metabolites, leaving metabolites bound to cellular macromols. The level of bound metabolites was 1.5 times higher in the nasal mucosa than in the liver of the [2'-14C]I monkey. Levels of bound metabolites were similar in the liver of I- and II-treated monkeys. Apparently, the liver and nasal mucosa of C. jacchus can activate I and II to alkylating species. Unbound metabolites present in the liver, lung, kidneys, eye, blood and urine were extd. and sepd. by HPLC. Hydroxylation of the .alpha.-C to the N-nitroso group of I were the major metabolic pathways. Unmetabolized I was the major radioactive component in the liver, lung, eye, and blood. Redn. of the carbonyl of II yields 4-(methylnitrosamino)-1-(3-pyridyl)butan-1-ol (III) [76014-81-8]. III was present in all tissues analyzed, and the major radioactive component in the eye and stomach lumen. III was also excreted in the urine. II and III were metabolized by .alpha.-C hydroxylation. Apparently, in C. jacchus, i, II, and III are activated by alkylating species by .alpha.-C hydroxylation. In the 3rd monkey injected with II, DNA methylation was obsd. in the liver and nasal mucosa but not in the lung and kidneys. Pulmonary tissues of C. jacchus, unlike those of F344 rats, do not have the enzyme capacities to activate II to methylating species.
IT 4192-31-8 ***5980-06-3*** 15569-97-8 75195-76-5 76014-83-0
(as nitrosonornicotine metabolite, in marmoset monkey)

L3 ANSWER 8 OF 24

2022154763

AN CA102(21):180286d

AU Carmella, Steven G.; Hecht, Stephen S.

TI High-performance liquid chromatographic analysis of metabolites of the nicotine-derived nitrosamines, N'-nitrosonornicotine and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone

SO Anal. Biochem., 145(2), 239-44

AB An improved high-performance liq. chromatog. system was developed for the sepn. of 11 metabolites of the nicotine-derived nitrosamines N'-nitrosonornicotine (NNN)(I) [16543-55-8] and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK)(II) [64091-91-4]. The new system employed a 5-.mu.m octadecylsilane bonded column eluted with aq. NaOAc-MeOH gradients of varying pH. Anal. times were typically 30 min for NNN metabolites and 50 min for NNK metabolites, compared to 80 and 90 min, resp., when 10-.mu.m columns were used. The E and Z isomers of all nitrosamine-contg. metabolites of NNK were sepd. The chromatog. behavior of the 11 metabolites as well as NNN and NNK was studied between pH 4.0 and 7.5. The retention times of several metabolites were altered significantly as a function of pH. The results of the pH study provide valuable addnl. criteria for metabolite identification as well as optimized conditions for their sepn. Applications of the system to the metab. of [2'-14C]NNN in cultured rat esophagus and [carbonyl-14C]NNK in rat liver slices are presented.

IT 532-12-7 4192-31-8 ***5980-06-3*** 15569-97-8 16543-55-8 16543-55-8D, metabolites 53798-73-5 59578-62-0 64091-91-4 64091-91-4D, metabolites 75195-76-5 76014-81-8 76014-82-9 76014-83-0 85352-99-4
(detn. of, by HPLC)

L3 ANSWER 9 OF 24

AN CA99(5):34203c

AU Castonguay, Andre; Lin, Dorothy; Stoner, Gary D.; Radok, Patti; Furuya, Keizo; Hecht, Stephen S.; Schut, Herman A. J.; Klaunig, James E.

TI Comparative carcinogenicity in A/J mice and metabolism by cultured mouse peripheral lung of N'-nitrosonornicotine, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone, and their analogs

SO Cancer Res., 43(3), 1223-9

AB The tumorigenic activities in A/J mouse lung of the tobacco-specific nitrosamines N'-nitrosonornicotine (NNN)(I) [16543-55-8], 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK)(II) [64091-91-4], and their metabolites retaining the nitroso group were studied, and the metab. of NNN and NNK in cultured mouse peripheral lung was investigated. A total dose of 0.12 mmol of each NNN metabolite was given in 22 i.p. injections to each A/J mouse. Thirty weeks after the last injection, the no. of lung tumors/animal induced was: NNN, 1.2; 3'-hydroxy-N'-nitrosonornicotine

[75195-74-3], 0.2; 4'-hydroxy-N'-nitrosonornicotine [75195-75-4], 1.6; and N'-nitrosonornicotine 1-N-oxide [75195-76-5], 0.8. [2',5',5'-Trideutero]-N'-nitrosonornicotine, an .alpha.-trideutero analog of NNN, induced 1.5 lung tumors/animal. In cultured mouse peripheral lung, the major metabolic pathways of [2'-14C]NNN were 2'- and 5'-C hydroxylation. Pyridine N-oxidn. and N-denitrosation were also obsd. to a minor extent. Therefore, 3'-hydroxylation, 4'-hydroxylation, and N-oxidn. are not involved in the metabolic activation of NNN in A/J mouse lung. A total dose of 0.10 mmol of NNK induced 37.6 lung tumors/animal. Two of its metabolites, 4-(methylnitrosamino)-1-(3-pyridyl)butan-1-ol (NNAI) [76014-81-8] (26.3 tumors/animal) and 4-(methylnitrosamino)-1-(3-pyridyl-N-oxide)-1-butanone [76014-82-9] (3.6 tumors/animal), were less potent than was NNK. A few nasal cavity and liver tumors were also obsd. in the NNK- and NNAI-treated groups. In cultured peripheral lung, [1-14C]NNK was rapidly converted to [1-14C]NNAI, and both of these nitrosamines were metabolized by .alpha.-C hydroxylation. Radioautog. of explants treated with [2'-14C]NNN or [1-14C]NNK showed higher labeling of the bronchi than of the parenchyma. Thus, NNN and NNK can be metabolized by .alpha.-C hydroxylation in A/J mouse lung where most tumors are obsd.

IT 532-12-7 4192-31-8 ***5980-06-3*** 15569-97-8 16543-55-8D, metabolites 20971-79-3 53798-73-5 59578-62-0 64091-91-4D, metabolites 75195-74-3 75195-75-4 75195-76-5 76014-80-7 76014-81-8 76014-82-9 76014-83-0 85352-99-4
(carcinogenicity of, in lung)

L3 ANSWER 10 OF 24

AN CA96(7):47428t

AU Hecht, Stephen S.; Chen, Chi Hong B.; Young, Ruth; Hoffmann, Dietrich

TI Chemical studies on tobacco smoke. LXXI. Mass spectra of tobacco alkaloid-derived nitrosamines, their metabolites, and related compounds

SO Beitr. Tabakforsch. Int., 11(2), 57-66

AB The mass spectra of the tobacco alkaloid-derived nitrosamines N'-nitrosonornicotine (I) [16543-55-8], 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (II) [64091-91-4], 4-(methylnitrosamino)-4-(3-pyridyl)butanal [64091-90-3], N'-nitrosoanabasine [1133-64-8], and N'-nitrosoanatabine [71267-22-6] and of known mammalian metabolites of I and II are presented. Mass spectra of synthetic derivs. related to these nitrosamines and their metabolites are also included. These spectra will be useful in studies on the occurrence and metab. of the tobacco alkaloid-derived nitrosamines and in investigations of other compds. related to the tobacco alkaloids.

IT 1133-64-8 4192-31-8 ***5980-06-3*** 15569-97-8 16543-55-8
24966-13-0 53798-73-5 64091-90-3 64091-91-4 68743-64-6
68743-65-7 68743-68-0 71267-22-6 75195-74-3 75195-78-7
75195-79-8 75195-86-7 76014-80-7 76014-81-8 76014-82-9
76014-83-0 78246-24-9 80508-17-4 80508-18-5 80508-20-9
80508-21-0 80508-22-1 80508-23-2 80508-24-3
(of tobacco smoke, mass spectra of)

L3 ANSWER 11 OF 24

AN CA96(1):1853z
AU Hecht, Stephen S.; Lin, Dorothy; Chen, Chi Hong B.
TI Comprehensive analysis of urinary metabolites of N'-nitrosonornicotine
SO Carcinogenesis (London), 2(9), 833-8
AB The urinary metabolites of N'-nitrosonornicotine (I) [16543-55-8] were detd. by simple high-pressure liq. chromatog. method. The percentage excretion of the principal urinary metabolites was detd. over a dose range of 3-300 mg/kg in the F-344 rat, as follows: 4-hydroxy-4-(3-pyridyl)butyric acid [15569-97-8] (37.1-53.3%, resp., of the dose), N'-nitrosonornicotine 1-N-oxide [75195-76-5] (6.7-10.7'%), norcotinine [5980-06-3] (3.2-5.1%), 4-oxo-4-(3-pyridyl)butyric acid [4192-31-8] (31.1-12.8%), N'-nitrosonornicotine [16543-55-8] (3.3-5.2%). In the strain A mouse and Syrian golden hamster, the urinary metabolites were qual. similar to those obsd. in the F-344 rat. The interrelations of the various metabolites of I which were obsd. in vitro and in vivo were established. The in vitro metabolites resulting from 2'-hydroxylation by liver microsomes, myosmine [532-12-7] and 4-hydroxy-1-(3-pyridyl)-1-butanone [59578-62-0] were converted, by the F-344 rat, primarily to 4-oxo-4-(3-pyridyl)butyric acid as a urinary metabolite. The in vitro metabolite resulting from 5'-hydroxylation by liver microsomes, 2-hydroxy-5-(3-pyridyl)tetrahydrofuran [53798-73-5], gave 4-hydroxy-4-(3-pyridyl)butyric acid as its major urinary metabolite, apparently via 5-(3-pyridyl)-tetrahydrofuran-2-one. N'-Nitrosonornicotine 1-N-oxide, the remaining major in vitro metabolite, was excreted to a large extent unchanged in F-344 rat urine. The urinary metabolites from 2'-hydroxylation and 5'-hydroxylation of I, 4-oxo-4-(3-pyridyl)butyric acid and 4-hydroxy-4-(3-pyridyl)butyric acid, resp., were not formed from the in vivo metabolite norcotinine and were not interconverted significantly by the F-344 rat. Thus, these metabolites are reliable indicators for the 2 possible in vivo .alpha.-hydroxylations of I.
IT 532-12-7 4192-31-8 ***5980-06-3*** 15569-97-8 16543-55-8
53798-73-5 59578-62-0 75195-76-5
(as nitrosonornicotine metabolite, in urine)

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L3 ANSWER 12 OF 24
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AN CA92(9):70775e
AU Chen, Chi-Hong B.; Fung, Ping T.; Hecht, Stephen S.
TI Assay for microsomal .alpha.-hydroxylation of N'-nitrosonornicotine and determination of the deuterium isotope effect for .alpha.-hydroxylation
SO Cancer Res., 39(12), 5057-62
AB A high-pressure liq. chromatog. assay was developed for microsomal .alpha.-hydroxylation (2'-hydroxylation and 5'-hydroxylation) of N'-nitrosonornicotine (I) [16543-55-8]. I was incubated with rat liver microsomes and a NADPH-generating system at 37.degree.. After addn. of 2,4-dinitrophenylhydrazine reagent, the mixts. were analyzed by reverse-phase high-pressure liq. chromatog. The 2,4-dinitrophenylhydrazones of 4-hydroxy-1-(3-pyridyl)-1-butanone and 4-hydroxy-1-(3-pyridyl)butanal were quantitied by UV light detection at 254 nm. Km'S for 2'-hydroxylation and 5'-hydroxylation of I by liver microsomes from Aroclor-treated male F-344 rats were 1.81 and 1.96 mM, while Vmax's were 0.53 and 1.05 nmol/min/mg protein, resp. Aroclor pretreatment of rats resulted in a 20-fold induction of 2'-hydroxylation, but only a 1.9-fold induction of 5'-hydroxylation. The D isotope effect fo .alpha.-hydroxylation of I was detd. by comparing the rates of 2'-hydroxylation and 5'-hydroxylation of I, N'-nitrosonornicotine-2',5',5'-d2 [72614-69-8], N'-nitrosonornicotine-2'-d2 [72614-70-1], and nN'-nitrosonornicotine-5',5'-d2 [72614-72-3]. The D isotope effect (VmaxH/VmaxD) was 2.4-2.7 for 5'-hydroxylation and 1.2 for 2'-hydroxylation.
IT 532-12-7 ***5980-06-3***
(deuteration of)

L3 ANSWER 13 OF 24
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AN CA89(13):99608b
AU McKennis, Herbert, Jr.; Bowman, Edward R.; Yi, J. Mark; Sprouse, C. T.
TI Participation of pyridine-N-oxides in the metabolism of nicotine in vivo. A preliminary study
SO Biol. Oxid. Nitrogen, Proc. Int. Symp., 2nd, Meeting Date 1977, 163-8. Edited by: Gorrod, John W. Elsevier: Amsterdam, Neth.
AB After oral administration of nicotine (I) [54-11-5] metabolites (S)-cotinine [486-56-6] and (S)-cotinine N-oxide [67445-82-3] (570 and 535 mg/kg, resp.) to monkeys, demethylcotinine [5980-06-3], 3-hydroxycotinine [34834-67-8], and allohydroxycotinine [37096-14-3] were isolated from the urine as metabolites. In the rabbit, administration of 3-pyridylacetic acid N-oxide [67445-83-4] produced the urinary metabolites 3-pyridylacetic acid [501-81-5]

and N-(3-pyridylacetyl)glycine [6434-22-6].
IT ***5980-06-3*** 34834-67-8 37096-14-3
(as cotinine metabolite)

L3 ANSWER 14 OF 24
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AN CA89(7):59994t
AU Glenn, David F.; Edwards, William B., III
TI Synthesis and mass spectrometry of some structurally related nicotinoids
SO J. Org. Chem., 43(14), 2860-70
AB Structurally related nicotinoids I (R = 2-, 3-, 4-pyridyl; R1 = Me, H, CHO), II and III (R = 2-, 3-, 4-pyridyl. were prepd. and their mass spectra detd. Thus, II (R = 2-pyridyl) was prepd. by cyclizing cyclopropyl 2-pyridyl ketone with HCONH2. Their complex electron-induced fragmentation mechanisms are discussedon the basis of 27 site-labeled D analogs, high-resoln. measurements, and metastable ion studies.
IT 54-11-5 486-56-6 494-97-3 5860-66-2 ***5980-06-3*** 23950-04-1
(mass spectrum of)

L3 ANSWER 15 OF 24
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AN CA87(21):161367m
AU Yi, J. Mark; Sprouse, C. T.; Bowman, Edward R.; McKennis, Herbert, Jr.
TI The interrelationship between the metabolism of (S)-cotinine-N-oxide and (S)-cotinine
SO Drug Metab. Dispos., 5(4), 355-62
AB The metab. of (S)-cotinine-N-oxide (I) [36508-80-2] was studied in the rabbit and the dog. The pattern of Koenig-pos. substances in the urine of the animals suggested the presence of S-cotinine [486-56-6], S-demethylcotinine [5980-06-3], hydroxycotinine [27323-64-4], and allohydroxycotinine [713-05-3], compds. previously identified as metabolites of (S)-cotinine and (S)-nicotine in many mammalian species. In the dog, 34% of the administered oral dose of (S)-cotinine-N-oxide was recovered from the urine, and 21% was recovered from the urine of the rabbit. Confirmation of the presence of (S)-cotinine, (S)-demethylcotinine, hydroxycotinine, and allohydroxycotinine in the urine of the rabbits was obtained by isolation of the metabolites as themselves or as derivs. The data, although establishing the possibilities of an intermediary role for (S)-cotinine-N-oxide in the metab. of nicotine, do not clearly indicate whether the metabolites such as demethylcotinine arise via the route (S)-cotinine-N-oxide .fwdarw. (S)-cotinine .fwdarw. (S)-demethylcotinine or via the alternate route (S)-cotinine-N-oxide

.fwdarw. (S)-demethylcotinine-N-oxide .fwdarw. (S)-demethylcotinine.

IT 486-56-6 713-05-3 ***5980-06-3*** 27323-64-4 64354-88-7
(as cotinine oxide metabolite)

L3 ANSWER 16 OF 24

AN CA86(17):115687x

AU Schumacher, Joseph N.; Green, Charles R.; Best, Freddie W.; Newell, Marjorie P.

TI Smoke composition. An extensive investigation of the water-soluble portion of cigarette smoke

SO J. Agric. Food Chem., 25(2), 310-20

AB Smoke condensate from 70 mm nonfiltered cigarets smoked under std. conditions was collected in dry ice cooled traps and partitioned between ether and water. The water-sol. portion (.apprx.38%) was chromatographed with gradient solvent systems on silicic acid to give 9 fractions. Further sepn. of these fractions by gas chromatog. permitted isolation of 479 components. Identifications of most of these components were based on IR, mass, and NMR spectra, and gas chromatog. retention times, and comparison of these data with those of authentic samples. Of the 479 isolates identified, 387 are reported for the first time as tobacco smoke components; these include 19 acids, 61 lactones, 32 esters, 41 amides, 21 imides, 45 aldehydes and ketones, 45 alcs., 30 pyridine derivs., 25 imidazoles, 31 lactams, 23 miscellaneous nitrogen heterocyclic compds., and 14 miscellaneous compds.

IT 50-21-5, biological studies 51-17-2D, alkyl derivs. 54-11-5 55-21-0 56-81-5, biological studies 57-10-3, biological studies 57-55-6, biological studies 58-08-2, biological studies 60-12-8 60-35-5, biological studies 64-19-7, biological studies 65-85-0, biological studies 67-47-0 75-12-7, biological studies 75-86-5 78-51-3 78-97-7 78-98-8 79-05-0 79-06-1, biological studies 79-09-4, biological studies 79-10-7, biological studies 79-16-3 79-20-9 79-31-2 79-39-0 79-41-4, biological studies 80-71-7 83-33-0 83-67-0 84-66-2 84-74-2 88-14-2 91-10-1 92-48-8 92-61-5 93-51-6 95-48-7, biological studies 95-71-6 96-24-2 96-35-5 96-48-0 96-49-1 97-64-3 98-00-0 98-01-1, biological studies 98-92-0 99-06-9, biological studies 99-96-7, biological studies 100-51-6, biological studies 100-79-8 102-93-2 103-81-1 103-82-2, biological studies 104-21-2 105-43-1 106-44-5, biological studies 107-18-6, biological studies 107-21-1, biological studies 107-41-5 107-92-6, biological studies 108-27-0 108-28-1 108-30-5, biological studies 108-31-6, biological studies 108-32-7 108-61-2 108-95-2, biological studies 108-99-6 109-00-2 109-00-2D, alkyl derivs. 109-52-4, biological studies 109-97-7 110-13-4 110-61-2 110-86-1D, derivs. 110-98-5 111-46-6, biological studies 114-33-0 116-09-6 116-53-0 117-81-7

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118-71-8 119-84-6 120-80-9, biological studies 121-33-5
121-34-6 123-31-9, biological studies 123-39-7 123-56-8
123-76-2 126-33-0 127-17-3, biological studies 128-37-0,
biological studies 131-16-8 134-81-6 141-78-6, biological
studies 142-08-5 274-45-3 288-32-4, biological studies
288-32-4D, derivs. 350-03-8 461-72-3 480-91-1 484-73-1
486-56-6 486-84-0 488-93-7 490-78-8 496-63-9 497-06-3
497-23-4 498-07-7 501-52-0 503-66-2 503-74-2 504-63-2
517-23-7 529-34-0 532-12-7 541-35-5 541-46-8 541-47-9
542-28-9 542-59-6 556-52-5 563-83-7 565-70-8 581-46-4
581-50-0 590-90-9 591-11-7 592-20-1 609-38-1 615-15-6
616-03-5 616-45-5 616-47-7 620-02-0 625-37-6 625-38-7
626-97-1 627-69-0 628-02-4 631-66-3 634-97-9 637-88-7
640-06-2 644-46-2 646-07-1 675-20-7 692-33-1 694-85-9
765-69-5 766-36-9 766-39-2 766-45-0 770-39-8 822-36-6
822-90-2 823-36-9 823-82-5 872-50-4, biological studies
875-80-9 930-62-1 930-68-7 931-20-4 931-40-8 1003-29-8
1003-56-1 1003-68-5 1072-83-9 1072-87-3 1073-26-3
1073-96-7 1113-57-1 1117-74-4 1119-29-5 1119-49-9
1121-05-7 1121-07-9 1121-19-3 1121-25-1 1121-78-4
1121-89-7 1122-43-6 1187-58-2 1192-79-6 1193-79-9
1194-97-4 1300-71-6 1452-77-3 1490-04-6 1575-46-8
1587-15-1 1617-31-8 1617-32-9 1687-64-5 1823-90-1
1917-15-3 2302-39-8 2346-26-1 2381-87-5 2503-46-0
2524-90-5 2745-26-8 2758-18-1 2935-44-6 3059-71-0
3128-06-1 3233-32-7 3279-76-3 3284-51-3 3552-33-8
3718-67-0 3724-65-0 3727-35-3 3760-54-1 3779-64-4
3878-55-5 3885-29-8 4030-18-6 4030-22-2 4030-23-3
4030-24-4 4100-80-5 4160-77-4 4272-12-2 4435-50-1
4437-50-7 4551-72-8 5058-01-5 5129-72-6 5264-15-3
5331-48-6 5341-95-7 5371-49-3 5469-16-9 5597-50-2
5615-90-7 5625-53-6 5768-79-6 5803-57-6 5834-16-2
5896-02-6 5953-51-5 5979-92-0 5979-94-2 ***5980-06-3***
(of tobacco smoke condensate)

L3 ANSWER 17 OF 24

AN CA86(5):26686d
AU McLachlan, John A.; Dames, Nancy M.; Sieber, Susan M.; Fabro, Sergio
TI Accumulation of nicotine in the uterine fluid of the six-day pregnant rabbit
SO Fertil. Steril., 27(10), 1204-13
AB In 6-day pregnant rabbits dosed i.v. with 3-labeled nicotine (I) [54-11-5] the 3H-activity in the uterine fluid was approx. 5-11 times greater than that in the plasma at the corresponding times; 3H-I itself accounted for most of this radioactivity. DDT [50-29-3] also accumulated in the uterine luminal fluid of 6-day pregnant rabbits, but to a lesser extent. However, I or DDT accumulation did

not occur in similarly treated, nonpregnant rabbits. The radioactivity in the uterine fluid of rabbits treated with 14C-labeled isoniazid [54-85-3], salicylic acid [69-72-7], barbital [57-44-3], antipyrine [60-80-0], and caffeine [58-08-2] was not different from that in the plasma (uterine fluid to plasma radioactivity ratios ranged between 0.67 and 1.85) in both 6-day pregnant and nonpregnant rabbits. No differences in regard to I metab., vol. of distribution, plasma disappearance, plasma protein binding, or urinary excretion were found between 6-day pregnant and nonpregnant rabbits. Accumulation of I took place in the uterine luminal fluid of nonpregnant does pretreated with either progesterone or human chorionic gonadotropin, but did not occur in does pretreated with estrogen. It is possible that the accumulation of I in uterine fluid of pregnant does and in human chorionic gonadotropin- or progesterone-pretreated nonpregnant does is due to the binding of I to specific uterine fluid proteins.

IT 50-29-3, biological studies 54-11-5 54-85-3 57-44-3 58-08-2, biological studies 60-80-0 69-72-7, biological studies 486-56-6 ***5980-06-3*** 9004-54-0, biological studies
(of uterus luminal fluid, in pregnancy)

L3 ANSWER 18 OF 24
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AN CA86(1):715n

AU Pilotti, Ake; Enzell, Curt R.; McKennis, Herbert, Jr.; Bowman, Edward R.; Dufva, Eva; Holmstedt, Bo

TI Studies on the identification of tobacco alkaloids, their mammalian metabolites and related compounds by gas chromatography-mass spectrometry

SO Beitr. Tabakforsch., 8(6), 339-49

AB Gas chromatog. and mass spectrometry, using multiple ion detection, was performed on nicotine (I) [54-11-5], I metabolites, and other tobacco smoke constituents in order to provide a basis for study of I metab. Chromatog. data are given for 30 tobacco alkaloids. The acidic I metabolites were chromatographed as the Me esters. The thermally unstable quaternary ammonium compmds. were examd. using the direct inlet system. I levels were detd. in blood plasma from 2 cigaret smokers.

IT 486-56-6 487-19-4 491-26-9 494-52-0 494-97-3 532-12-7 1129-68-6 2055-29-0 3000-74-6 4192-31-8 ***5980-06-3*** 15585-43-0 17270-45-0 17270-50-7 24380-92-5 33952-07-7 36508-80-2 61192-46-9 61301-99-3
(gas chromatog. and mass spectrometry of, as tobacco constituent)

L3 ANSWER 19 OF 24
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AN CA85(11):73227u

AU Harke, Hans P.; Frahm, Barbara
TI Nicotine metabolism in the pig
SO Toxicology, 6(1), 125-8
AB After i.v. injection of 0.33 mg nicotine (I) [54-11-5]/kg to pigs, the elimination of unchanged I as well as nicotine-N-oxide [2820-55-5], cotinine [486-56-6], nornicotine [494-97-3] and norcotinine [5980-06-3] was detd. in the urine. In female pigs 16.3% and male pigs 25.9% of the applied I were recovered as the metabolites within 13 hr. No significant amt. of I was detected in urine 8 hr after treatment. Nicotine-N-oxide and cotinine were the main degrdn. products of I, and a significant amt. of these metabolites was found in urine even at 8-23 hr after application.
IT 486-56-6 494-97-3 2820-55-5 ***5980-06-3***
(as nicotine metabolite, in urine)

L3 ANSWER 20 OF 24

AN CA83(25):201713x
AU Turner, D. M.; Armitage, A. K.; Briant, R. H.; Dollery, C. T.
TI Metabolism of nicotine by isolated perfused dog lung
SO Xenobiotica, 5(9), 539-51
AB Nicotine (I) [54-11-5] (50 .mu.g every 30 sec for 10 min) administered via the pulmonary artery and in cigaret smoke to the isolated perfused dog lung prepn. was converted to nicotine 1'-oxide (II) [491-26-9] and cotinine (III) [486-56-6] was detected in the venous blood. II, III, and demethylcotinine [5980-06-3] were detected when I was administered in smoke to a closed circuit lung prepn.
IT 486-56-6 491-26-9 ***5980-06-3***
(as nicotine metabolite, in lung)

L3 ANSWER 21 OF 24

AN CA83(9):74865w
AU Harke, H. P.; Mauch, A.; Frahm, B.
TI Thin-layer chromatographic determination of nicotine and nicotine metabolites in urine
SO Fresenius' Z. Anal. Chem., 274(4), 300
AB Thin-layer chromatog. was employed to det. urinary concns. of nicotine, cotinine, nicotine N-oxide, nornicotine, and dimethylcotinine. Alkalinized urine was extd. with Et2O. The aq. phase contg. nicotine N-oxide was reduced with TiCl3, and the resulting nicotine and accompanying cotinine were extd. with CHCl3. The Et2O and CHCl3 exts. were evapd., and the nicotine and metabolites isolated from other urine constituents by thin-layer chromatog. on Kieselgel-60 F254. Nicotine and its metabolites were converted to colored compds. by treatment of the gel with BrCN and

4-chloraniline. The colored sections were removed, extd., and the concn. of nicotine metabolites detd. spectrometrically. In control expts. with pig urine contg. added nicotine and metabolites, recoveries were 81-89%. At 480 nm the relation between concn. and extinction was linear. By controlling conditions, 5-50 .mu.g nicotine were detd. readily.

IT 54-11-5 486-56-6 494-97-3 2820-55-5 ***5980-06-3***
(detn. of, in urine, thin-layer chromatog.)

L3 ANSWER 22 OF 24
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AN CA82(17):107352m
AU Harke, H. P.; Schueller, D.; Frahm, B.; Mauch, A.
TI Demethylation of nicotine and cotinine in pigs
SO Res. Commun. Chem. Pathol. Pharmacol., 9(4), 595-9
AB Demethylcotinine [5980-06-3] was detected in urine of pigs following i.v. injection of nicotine (I) [54-11-5], and cotinine [486-56-6] (both at 0.33 mg/kg). An addnl. demethylation product, nornicotine [494-97-3] was found following application of nicotine. Thus, nicotine is metabolized in pigs by enzymatic oxidn. or demethylation.
IT ***5980-06-3***
(as nicotine and cotinine metabolite)

L3 ANSWER 23 OF 24
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AN CA81(25):164262k
AU Harke, H. P.; Chevalier, H. J.; Frahm, B.
TI Nicotine metabolism in swine
SO Experientia, 30(8), 883-4
AB Oxidative metab. of nicotine (I) [54-11-5] to cotinine [486-56-6] and nicotine N-oxide [2820-55-5] and demethylation of I to nornicotine [494-97-3] and norcotinine [5980-06-3] were obsd. in I-injected swine. Swine treated i.v. or i.p. with 1.8 mg I excreted 5% of the I as unchanged I, 10% as nicotine N-oxide, and 3% as cotinine, nornicotine, and norcotinine in the urine within 6 hr after administration.
IT 486-56-6 494-97-3 2820-55-5 ***5980-06-3***
(formation of, as nicotine metabolite, in swine)

L3 ANSWER 24 OF 24
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AN CA72(21):109316v
AU Stalhandske, Torbjorn
TI Metabolism of nicotine and cotinine by a mouse liver preparation
SO Acta Physiol. Scand., 78, 236-48

2022154773

AB The metabolism of nicotine and cotinine by a 10,000 .times. g supernatant fr action of mouse liver homogenate was studied by using 14C-labeled compds. The metabolism of nicotine was TPNH and O2 dependent and chromatographical evidence for the formation of cotinine, .gamma.-(3-pyridyl)-.gamma.-oxo-N-methyl-butyramide (I) and hydroxycotinine are presented. Three un-identified metabolites and 14CO2 were also observed. The ob-served metabolites were also excreted in urine after i.p. administration of nicotine. Chromatographic evidence revealed that cotinine is metabolized to hydroxycotinine, I and (or) demethyl-cotinine and one unidentified metabolite. No formation of 14CO2 was observed.

IT ***5980-06-3***
(as cotinine metabolite)