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AN IMPROVED PROCEDURE FOR THE SYNTHESIS OF 3-IODO-2,4,6-TRIMETHYLPHENYL CARBAMOYLMETHYL-IMINODIACETIC ACID: AN EFFICIENT COMPLEX AGENT FOR ^{99m}Tc

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SUMMARY

The synthesis of 3-iodo-2,4,6-trimethylphenyl-carbamoylmethyl-iminodiacetic acid by a modified procedure is described. Its spectroscopic properties as well as its ^{99m}Tc complexing capacity are also presented.

Key Words: 3-iodo-2,4,6-trimethylphenyl-carbamoylmethyl-iminodiacetic acid, synthesis, ^{99m}Tc-complex.

Since Harvey *et al.*(1) reported the synthesis of 2,6-dimethylphenyl-carbamoyl methyl-iminodiacetic acid and tested it as a ^{99m}Tc complex formation agent for the study of the hepatobiliary tract, other authors in an attempt to improve the properties of the above mentioned compound, prepared a considerable number of iminodiacetic acid derivatives. Among them, 2,6-diethyl- and 2,6-diisopropyl phenyl-carbamoylmethyl-iminodiacetic acids resulted the most preferred complex formation agents, and were commercially available as diethyl-HIDA (EIDA) and diisopropyl-HIDA (DISOFENIN) respectively.

The preparation of HIDA derivatives, aimed at the finding of the best biological activity, followed a non scientifically stricted approach because of the poor knowledge about the physicochemical process involved in their metabolic elimination. In 1982, Nunn *et al.*(2) reported the preparation of 33 new HIDA derivatives, establishing that the 3-bromo-2,4,6-trimethylphenyl-carbamoylmethyl-iminodiacetic acid, known as MEBROFENIN, presented excellent biological properties. Kligensmith *et al.* (3) tested MEBROFENIN-^{99m}Tc and DISOFENIN-^{99m}Tc finding that the former complex showed a lower renal excretion level; on the other hand, both complexes presented similar properties regarding

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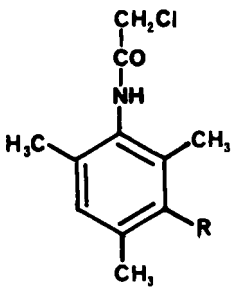
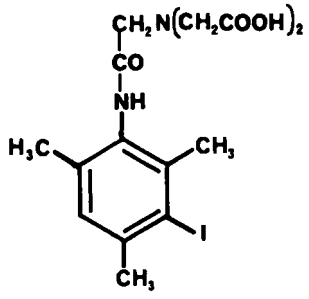
hepatocite extraction efficiency, time of maximal radioactivity in liver, and washing of the hepatic parenchyma.

Subramanian et al. (4) prepared a product similar to MEBROFENIN but changing the halogen on the aromatic ring. Thus, the iodo-analogous of MEBROFENIN when tested as a ^{99m}Tc transporter gave better results than the bromo-derivative because of its almost null renal excretion.



1: R=H

2: R=I



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Due to the superior properties of this complex, we attempted the synthesis of the 3-iodo-2,4,6-trimethylphenyl-carbamoylmethyl-iminodiacetic acid following an approach previously reported for the synthesis of HIDA-derivatives (5). We wish to report here that in our conditions the title compound was prepared in better yield than that described which resulted 27% when starting from the free aniline derivative.

RESULTS

Our pathway to the synthesis of the title product started with 2,4,6-trimethyl aniline which upon reaction with chloroacetyl chloride in anhydrous conditions afforded the corresponding anilide 1 in 90% yield. When using aqueous-pyridine medium this compound was obtained in only 50% yield. Compound 1 was treated with iodine/potassium periodate yielding the iodo-derivative 2. Reaction of 2 with iminodiacetic acid in the conditions already described (5) gave the expected compound 3 with an overall yield of 41%. Its spectroscopic properties were in agreement with the proposed structure.

Following a known procedure, compound 3 was tested as ^{99m}Tc complex agent with excellent results.

EXPERIMENTAL

Melting points are uncorrected. ^1H-NMR spectrum was measured at 100.1 MHz with a Varian XL-100-15 FT-NMR spectrometer. Mass spectrum was determined at 70 eV (direct inlet) with a Varian-MAT CH7-A spectrometer interfaced to a Varian-MAT Data System 166 computer. Microanalysis was performed by UMYMFOR (CONICET-FCEN).

N-[2,4,6-Trimethylphenyl]-2-chloro-acetamide (1). A solution of 2,4,6-trimethylaniline (20.3 g, 150 mmol) and triethylamine (15 g, 150 mmol) in anhydrous CH_2Cl_2 (150 ml) was cooled to -30°C; to the stirred mixture, a solution of chloroacetyl chloride (18.6 g, 165 mmol) in CH_2Cl_2 (25 ml) was added dropwise keeping the temperature below -25°C. When the addition was over, the reaction mixture was allowed to warm to room temperature and stirred for 1 hr at this temperature. The solvent was removed, the precipitate was filtered off, washed with water and dried. Recrystallization from EtOH gave compound 1, m.p. 178°C (yield: 90%).

N-[3-Iodo-2,4,6-trimethylphenyl]-2-chloro-acetamide (2). Compound 1 (10.5 g, 50 mmol) was dissolved in a mixture of acetic acid (50 ml), water (10 ml), and conc. H_2SO_4 (1.5 ml). Under continuous stirring, KIO_4 (2.3 g, 20 mmol) and iodine (10.2 g, 80 mmol) were added and the reaction mixture was heated at 100°C for 45 min. After 30 min at room temp., acetic acid (25 ml) was added and stirred again for 30 min. Water (250 ml) was added and the excess of iodine was eliminated by addition of $NaSO_3H$ (0.25 g). The precipitate was filtered, washed with water and dried. It was recrystallized from abs. EtOH yielding 12.1 g (72%) of compound 2 of m.p. 180-182°C.

3-Iodo-2,4,6-trimethylphenyl-carbamoylmethyl-iminodiacetic acid (3). A mixture of compound 2 (10.1 g, 30 mmol), iminodiacetic acid (7.9 g, 60 mmol) was dissolved in EtOH-H_2O (185:40 ml) containing NaOH (4.8 g). To the stirred mixture, a solution of K_2CO_3 (2.0 g, 15 mmol) in H_2O (55 ml) was added dropwise to maintain an alkaline medium (pH 11). After 24 hr at room temperature the mixture was extracted with Et_2O (2 x 30 ml) which was discarded. The remaining aqueous phase was treated with conc. HCl to pH 2.5, and the precipitate was filtered off, washed with dil. HCl and dried. Recrystallization from EtOH gave compound 3 (8.2 g. 63%) of m.p. 222-224°C.

^{1}H-NMR (DMSO-d_6:TMS): 2.07 (s, 3H, $C\underline{H}_3Ph$), 2.28 (s, 3H, $C\underline{H}_3Ph$), 2.37 (s, 3H, $C\underline{H}_3Ph$), 3.49 (s, 2H, $COC\underline{H}_2N$), 3.56 (s, 4H, $NC\underline{H}_2COOH$), 7.10 (s, 1H, $\underline{H}Ph$), 9.58 (b.s., 2H, $COO\underline{H}$).

MS (m/z, %): 434 (M^+, 13), 416 (M-18, 54), 371 (416-45, 61), 261 ($C_9H_{12}NI$, 47), 146 ($C_5H_8NO_4$, 100), 134 (261-127, 20), 101 (146-45, 97).

Analysis: calc. for $C_{15}H_{19}N_2IO_5$, C: 41.47; H: 4.38; N: 6.45; I: 29.26
Found, C: 41.58; H: 4.62; N: 6.36; I: 29.23

Preparation of IODOFENIN-^{99m}Tc. Compound 3 (40 mg) was dissolved in 0.25N NaOH (0.9 ml) and diluted with H_2O (1 ml). To this solution, a solution of $SnCl_2$(10 mg Sn^{++}/ml in 1N HCl) (50 µl) was added with continuous stirring; the pH of the mixture was 5.8-6.0. To this, a solution of $Na^{99m}TcO_4$ (1 ml, 20 mCi) was added, and after 15 min the solution was controlled for radiochemical purity by ITLC (silica gel, MeOH-H_2O 85:15) and paper chromatography

($NaCO_3H$ 0.3 M-treated Whatman 1) developed with methyl-ethyl-ketone (6).
In all cases the radiochemical purity exceeded 90%.

REFERENCES

1. Harvey, E.B., Loberg, M.D. and Cooper, M.- *J. Nucl. Med.* 16: 533 (1975).
2. Nunn, A.D., Loberg, M.D. and Criley, R.A.- *J. Nucl. Med.* 24: 423 (1983).
3. Klingensmith, M., Fritzber, A. and Spitzer, V.- *Nucl. Med. Biol., Proc. III World Congress Nuclear Medicine and Biology*, Paris (1982).
4. Subramanian, G., Schneider, R.F. and McAfee, J.G.- *J. Lab. Compds. Radiopharm.* 19: 1463 (1982).
5. Mitta, A.E.A., Arciprete, C.P. and Gros, E.G.- *J. Lab. Compds. Radiopharm.* 19: 1602 (1982).
6. Mitta, A.E.A. and Robles, A.M. (editors) *Quality Control of Radiopharmaceuticals*, ALASBIMN (1987).