# Synthesis of $C^{14}$ Labelled Dimethylformamide and 3-(2-Aminobutyl-1-$C^{14}$)indole Acetic Acid Salt

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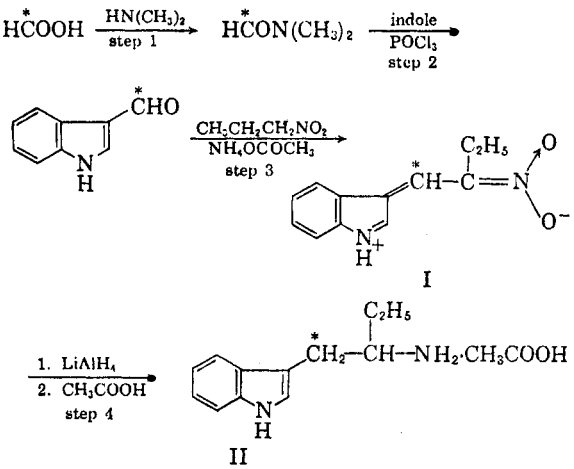
In connection with the interesting pharmacological[1] and clinical[2] findings concerning the activity of 3-(2-aminobutyl)-indole acetic acid salt (II)[3] we have synthesized this compound labelled with $C^{14}$ on $C_1$ of the butyl side chain according to the following sequence.




We chose the above synthesis rather than the Snyder and Katz[4] process as it was desirable to have a procedure applicable also to the preparation of 3-(2-amino-propyl) indole. Snyder and Katz[4] point out that their process gives a yield of only about 10% in the case of the gramine-nitroethane condensation.

Conversion of formic acid to dimethylformamide was briefly described,[5] but the preparation of radioactive dimethylformamide has not been reported. The remaining three steps were also reported previously.[6] As the present four-step procedure encompasses a number of improvements based on experimentation done subsequent to our publication[6] and contains some details of general interest, it appeared desirable to report it in detail.

## EXPERIMENTAL[7,8]

*Dimethylformamide-$C^{14}$.* The apparatus consisted of a 100-ml. two neck, round bottom flask, a glass inlet tube for dimethylamine, and a 40-cm. bulb condenser on top of which was placed a 12-cm. air-cooled condenser, which was attached to an 8-cm. downward cold water cooled condenser and a calibrated test tube attached to a Drierite tube. The rate of the flow of dimethylamine was measured with a flowmeter (Brooks-Rotameter Company, Lansdale, Pa.), tube 1A-15-1 (stainless steel float; the reading was 15.0 cm. which corresponds to 450 ml. of air per min. on the calibration curve).

Formic acid-$C^{14}$, 3.38 g. or 100 millicuries (96.5%, New England Nuclear Corporation), was diluted with 1.22 g. of nonradioactive formic acid (98+%, Eastman Kodak Company). Dimethylamine was passed under the surface of the liquid for a total of 3 hr. After 6 min. the initial fuming stopped, and the solution was heated on the steam bath. Water, heated by means of a constant temperature bath (58–59°), was passed through the bulb condenser from this time on using a circulating pump. The distillate amounted to 4.4 ml., and the crude product weighed 8.2 g.

The crude product was heated by means of an oil bath to 200°, and the distillate (1.0 ml.) was collected until the vapor temperature reached 105°. The residue weighed 6.5 g. and was shown by acid and base titrations to contain 1.1% of formic acid and 8.5% of salt (likely dimethylammonium formate). This crude dimethylformamide (specific activity = 0.80 millicuries per millimole) was used directly for the next experiment.

It is interesting to note that when a cold condenser was used very little dimethylformamide, if any, was formed. Also if no distillate was removed during the reaction, and a cold condenser was placed on top of the one which was heated, titration indicated 0.4% formic acid and 24.2% of the salt. The detailed mechanistic interpretation of this seemingly simple reaction would require a kinetic study which, due to lack of time, we were not able to perform.

*3-Indolecarboxaldehyde-$C^{14}$.*[9] Indole (2.13 g., 0.0182 mole) was dissolved in 1 ml. of the crude dimethylformamide. The remainder of the dimethylformamide was placed in a 100 ml. three neck flask, cooled in ice, and treated dropwise over a 20-min. period with 3.06 g. (0.02 mole) of phosphorus oxychloride. The indole solution was then added during 15 min. The yellow solution was stirred at room temperature for 2 hr. at which time it became orange. Ice (20 g.) was added, and the mixture was stirred for 5 min. when a clear red solution resulted. A solution of 3.8 g. of sodium hydroxide in 20 ml. of water was added during 15 min., and the oily suspension was refluxed for 4 min. The mixture was then cooled in ice, filtered, and washed well with water. The lumpy solid was transferred to a glass mortar, and it was powdered and transferred back into the sintered glass funnel. On trituration with ether (three times, total 10 ml.) a colorless solid resulted; 1.9 g. (72% yield) m.p. 193–195° (sl90°). Ultraviolet spectrum showed $\lambda_{max}$ 243 (13,500); 259 (11,500), 296 (13,050). These values compare very well with those of pure 3-indolecarboxaldehyde. Specific activity = 0.79 millicuries per millimole.

(1) M. E. Greig, R. A. Walk, and A. J. Gibbons, *J. of Pharmacology and Exp. Therap.*, **127**, 110 (1959); personal communication from M. E. Greig, J. H. Flokstra, and P. H. Seay.

(2) Symposium on Depression, its Diagnosis and Treatment, *J. Neuropsychiatry*, supplement in press.

(3) The trade name of the Upjohn Company for 3-(2-aminobutyl)-indole acetic acid salt is Monase.

(4) H. R. Snyder and L. Katz, *J. Amer. Chem. Soc.*, **69**, 3140 (1947).

(5) J. A. Mitchell and E. E. Reid, *J. Amer. Chem. Soc.*, **53**, 1879 (1931).

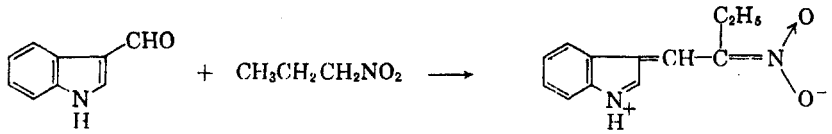
(6) R. V. Heinzelman, W. C. Anthony, D. A. Lyttle, and J. Szmuszkovicz, *J. Org. Chem.*, **25**, 1548 (1960).

(7) All melting points (capillary) are uncorrected. Ultraviolet spectra (in mμ) were determined in 95% ethanol using a Cary recording spectrophotometer, Model 14. Infrared spectra (in $cm.^{-1}$) were determined in Nujol using a Perkin-Elmer recording infrared spectrophotometer, Model 21. Counting was performed with a Packard Tri-Carb liquid scintillation spectrometer.

(8) The authors wish to thank Mr. W. A. Struck and his associates for the microanalyses, Mr. M. F. Grostic and Dr. R. W. Rinehart for the spectroscopic data, and Mr. L. G. Laurian for laboratory assistance.

(9) *Cf.* P. N. James and H. R. Snyder, *Org. Syntheses*, **39**, 30 (1959).

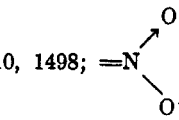
TABLE I



| Moles of 3-Indolecarboxaldehyde[a] | Moles of 1-Nitropropane | Moles of $NH_4OCOCH_3$ | Time of Heating,[b] Min. | Product M.P. | % Crude product obtained | % Purity by U.V.[c] | % Yield by U.V. |
|---|---|---|---|---|---|---|---|
| 0.069[d] | 0.224 | 0.026 | 60 | 116–119 | 73 | 67 | 49 |
| 0.069[e] | 0.224 | 0.026 | 75 | 133–134 | 66 | 96 | 63 |
| 0.0149[f] | 0.169 | 0.0056 | 75 | 133–134 | 74 | 93 | 69 |
| 0.0149[g] | 0.169 | 0.0056 | 75 | 124–132 | 58 | 93 | 54 |
| 0.0149[h] | 0.169 | 0.0056 | 55 | 118–160 | 73 | 67 | 49 |
| 0.0149[i] | 0.169 | 0.0056 | 75 | 120–129 | 56 | 87 | 49 |
| 0.0149[j] | 0.169 | 0.0056 | 75 | 121–130 | 55 | 82 | 45 |
| 0.069[k] | 0.67 | 0.0071[k] | 12 hr. | 133–134 | 37 | 94 | 35 |

[a] 3-Indolecarboxaldehyde was purchased from Aldrich and recrystallized once from ethanol. [b] All experiments were conducted on the steam bath. [c] The extinction coefficient at $\lambda_{max}$ 400 was used. [d] Nitrogen was not used and no distillate was removed. Some pure 3-indolecarboxaldehyde was obtained by working up the mother liquors. [e] Nitrogen was swept through the system and 5.2 ml. of distillate was collected during the reaction. The crude product was triturated with 20 ml. of ether and 5 ml. of petroleum ether (b.p. 30–60°). [f] Run the same way as described for the radioactive run; 4 ml. of distillate was collected. [g] Run the same way as described for the radioactive run; 5.5 ml. of distillate was collected. [h] Run the same way as described for the radioactive run, but at a faster rate of nitrogen (about double); 8 ml. of distillate was collected. [i] Nitrogen was not used and the mixture was stirred. At the end of the reaction 6 ml. was distilled *in vacuo*. [j] Nitrogen was not used and the mixture was not stirred. At the end of the reaction 6 ml. was distilled *in vacuo*. [k] Refers to moles of benzylamine. The solution was refluxed gently using an azeotropic separator. At the end it was cooled and the resulting solid was filtered and washed with petroleum ether (b.p. 30–60°).

As was observed previously[10] a considerable excess of dimethylformamide is essential in this reaction in order to secure a good yield. We have found that when 1:1.1 and 1:2 ratio of indole to dimethylformamide was used, the yield of 3-indolcarboxaldehyde was 21% and 31%, respectively.

3-(2-Acinitrobutylidene)-3*H*-pseudoindole, inner addition salt[11] (I). A 50-ml. three neck, round bottom flask was equipped with a stirrer, a joint for nitrogen inlet and a condenser set down for distillation attached to a 10 ml. graduated cylinder. The flask was charged with 3-indolecarboxaldehyde-$C^{14}$ (1.9 g. of radioactive and 0.25 g. of nonradioactive material; total 0.0149 mole), 0.43 g. (0.0056 mole) of ammonium acetate and 15 ml. (0.169 mole) of 1-nitropropane. Nitrogen was passed at the rate of 5.5–6.0 cm. (Brooks-Rotameter was used as described above), which corresponded to 110–150 ml. of air per min. The mixture was heated on the steam bath with stirring for 1 hr. 15 min. during which time 5.5 ml. of distillate was collected. The stirrer was moved above the surface of the solution and allowed to drain for a minute. The solution was then cooled in ice for 0.5 hr. while occasionally stirring with a spatula. The thick suspension was then filtered using the mother liquor to transfer. The solid was washed with water (3 × 5 ml.) and then with petroleum ether (b.p. 30–60°; 2 × 10 ml.) to give an orange powder; 2.3 g. (72% yield), m.p. 129–132°. This material was 99% pure by comparison of the extinction coefficient at $\lambda_{max}$ 400 mμ with that of the pure material (see below). Specific activity = 0.68 millicuries per millimole. An analytically pure sample of the nonradioactive material was obtained by crystallization from methanol, m.p. 134–135°. Ultraviolet spectrum showed $\lambda_{max}$ 219 (30,850), 277 (7,200), 283 (6,900), 400 (16,300). Infrared spectrum showed NH: 3310; =CH: 3040; C=N/C=C: 1630, 1590 sh, 1510, 1498;  : 1263 (vs), 1220 (vs); aromatic substitution: 742.

*Anal.* Calcd. for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.96. Found: C, 66.15; H, 5.40; N, 13.10 (residue 1.1%).

*3-(2-Aminobutyl-1-$C^{14}$)indole acetic acid salt* (II). A 100-ml. three neck round bottom flask was charged with 1.75 g. of lithium aluminum hydride and then 17 ml. of peroxide-free tetrahydrofuran. The mixture was stirred and refluxed under nitrogen for 0.5 hr. A solution of 2.3 g (0.0106 mole) of $C^{14}$-nitronate in 16 ml. of tetrahydrofuran was then added to the refluxing solution over a period of 70 min. The suspension was then refluxed for about 0.5 hr., the mixture was allowed to cool to room temperature, and the solid layer which accumulated around the top of the flask was scraped down with the aid of a bent spatula. Heating was then continued so that the total reflux time from the start of the addition was 5 hr. The mixture was cooled to room temperature and decomposed by the addition of a solution containing 1.7 ml. of water and 4.5 ml. of tetrahydrofuran during 15 min., followed by 1.8 ml. of 20% aqueous sodium hydroxide solution. All the solids were then scraped down into the solution, and the suspension was stirred for 0.5 hr. The mixture was filtered and the precipitate washed with tetrahydrofuran (2 × 10 ml.). Acetic acid (0.62 ml.) was added to the filtrate, and it was evaporated to dryness at <50° *in vacuo*. The resulting solid was triturated thoroughly with ethyl acetate, filtered, and washed with ethyl acetate, 1.85 g. (70.4% yield), m.p. 163–164°. Ultraviolet spectrum showed $\lambda_{max}$ 220 (36,450); sh 273 (5800); 281 (6200); 289.5 (5350). Infrared spectrum showed NH: 3300; $-NH_3^+$: 2750 sh, 2670, 2560, 2130; salt: 1630, 1568, 1525, 1420; C=C: 1496; aromatic substitution: 752 sh, 748. Specific activity: 0.70 millicuries per millimole.

(10) G. F. Smith, *J. Chem. Soc.*, 3842 (1954).

(11) *Cf.* E. H. P. Young, *J. Chem. Soc.*, 3493 (1958); A. S. F. Ash and W. R. Wragg, *J. Chem. Soc.*, 3887 (1958).

*Anal.* Calcd. for $C_{14}H_{20}N_2O_2$: C, 67.71; H, 8.12; N, 11.28. Found: C, 67.78; H, 8.20; N, 11.43.

An analytical sample of the nonradioactive material was obtained by crystallization from methanol-ethyl acetate, m.p. 166–167° (s 164°). The ultraviolet and infrared spectra were identical with those of the radioactive sample.

The radioactive sample was found to be homogeneous by paper chromatography in several solvent systems and radioautography of the paper chromatograms.[12]

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(12) F. S. Eberts, Jr., to be published.

## Resolution and Configuration of 1-(3-Hydroxy-3-phenylpropyl)-4-ethoxycarbonyl-4-phenylpiperidine

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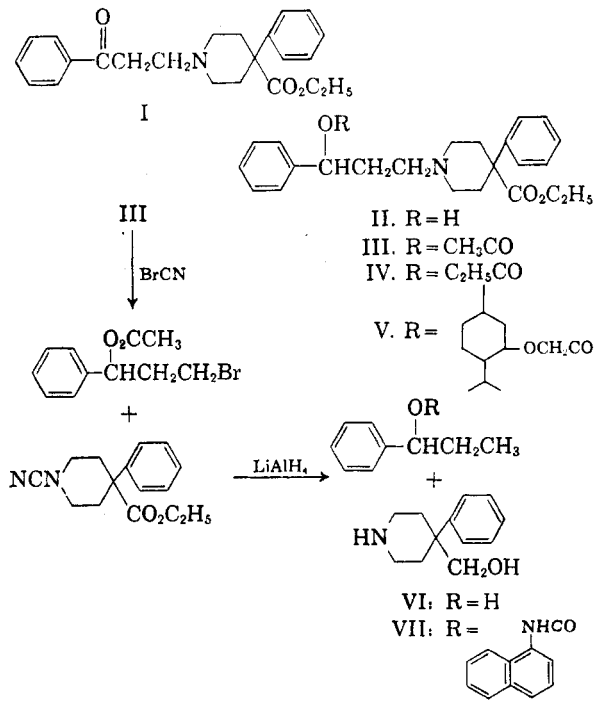
The discovery of the analgesic properties of 3-(4 - ethoxycarbonyl - 4 - phenylpiperidino)propiophenone (I)[1] prompted us to investigate the synthesis and pharmacologic evaluation of the corresponding alcohol, 1-(3-hydroxy-3-phenylpropyl)-4-ethoxycarbonyl-4-phenylpiperidine (II)[2a] and some of its derivatives. The carbinol II should exhibit greater stability than the ketone I (a Mannich base) and has the additional attraction that it is capable of resolution which might conceivably lead to a useful separation of analgesic and respiratory depressant activities usually associated with this type of analgesic.

Ketone I was conveniently reduced with sodium borohydride in aqueous ethanol to the desired carbinol II in high yield. The latter was crystalline and was characterized as the hydrochloride. The acetate III and propionate IV of the carbinol were also prepared. The oily esters were converted to crystalline maleates for analysis and testing.

Resolution of carbinol II proved difficult as none of the salts with the usual optically active acids could be induced to crystallize. A suitable derivative was eventually found by esterification with *l*-menthoxyacetyl chloride and formation of the crystalline maleate salt. Fractional crystallization yielded the *l*, *l*-ester maleate which liberated *l*-II on alkaline hydrolysis. The levo-base was characterized as the hydrochloride and converted to the levo-acetate maleate and levo-propionate maleate. Similarly, *d*-menthoxyacetyl chloride[3] was used to obtain *d*-II and its hydrochloride.

As a point of interest, the absolute configuration of levo-base II was determined. The *l*-acetate III was degraded by the von Braun cyanogen bromide method and the crude mixture reduced with lithium aluminum hydride. The chart shows the course of the reactions. The neutral fraction proved to contain *l*-ethylphenylcarbinol (VI) isolated as the α-naphthylurethan (VII) which had the same melting point and rotation as *l*-ethylphenylcarbinyl-α-naphthylurethane prepared from authentic *l*-ethylphenylcarbinol.[4] The latter has been shown to possess the S configuration.[5,6] Therefore, *l*-base II may be written as S-1-(3-hydroxy-3-phenylpropyl)-4-ethoxycarbonyl-4-phenylpiperidine.

The analgesic potencies[7] in mice of the various compounds are given in the table. An increase in analgesic activity was accompanied by an approximately corresponding increase in respiratory depression.




### EXPERIMENTAL

*1-(3-Hydroxy-3-phenylpropyl)-4-ethoxycarbonyl-4-phenylpiperidine hydrochloride* (II·HCl). Ketone I hydrochloride (12.0 g., 0.03 mole) was suspended in 48 ml. of 50% ethanol

(1) P. A. J. Janssen, A. H. M. Jageneau, P. J. A. Demoen, C. van de Westeringh, A. H. M. Raeymaekers, M. S. J. Wouters, S. Sanczuk, B. K. F. Hermans, and J. L. M. Loomans, *J. Med. Pharm. Chem.*, 1, 105 (1959).

(2*a*) Janssen and Eddy[2b] have recently reported carbinol II as its hydrochloride along with the corresponding acetate hydrochloride, III·HCl, and propionate hydrochloride, IV·HCl. Their analgesic potency values (mice) are in substantial agreement with those obtained in our laboratories.

(2*b*) P. A. J. Janssen and N. B. Eddy, *J. Med. Pharm. Chem.*, 2, 31 (1960).

(3) J. Read and W. J. Grubb, *J. Soc. Chem. Ind.*, 51, 329T (1932).

(4) P. A. Levene and L. A. Mikeska, *J. Biol. Chem.*, 70, 355 (1926).

(5) R. MacLeod, F. J. Welch, and H. S. Mosher, *J. Am. Chem. Soc.*, 82, 876 (1960).

(6) R. S. Cahn, C. K. Ingold, and V. Prelog, *Experientia*, 12, 81 (1956).

(7) N. B. Eddy and D. Leimbach, *J. Pharmacol.*, 107, 385 (1953).