catalyst bed was maintained at 500 ± 5°, and hydrogen at about 170 ml./min. and water at 6.5 g./hr. were fed continuously during the run. The contents of the receiver were extracted with 100 ml. of boiling xylene and the xylene-insoluble residue was recrystallized from boiling quinoline, to give 0.95 g. of fine light yellow crystals which darken without melting at about 470°.

Anal. Calcd. for $C_{18}H_{12}N_2$. C, 84.38; H, 4.69; N, 10.94. Found. C, 84.44; H, 4.72; N, 11.13.

(b) *From indole-3-aldehyde.* One gram of urorosein (II) prepared from indole-3-aldehyde according to Fearon and Boggust[10] was dissolved with warming in 150 ml. of ethanol; 25 ml. of water, 30 ml. of hydrochloric acid, and 5 g. of tin were added, and the mixture was kept for 2 days with occasional warming and addition of three 10-ml. increments of acid. The solvent containing suspended solids was decanted from undissolved tin, filtered, and the solid residue extracted on the filter with ethanol. The ethanol-insoluble residue was recrystallized from boiling quinoline to give 60 mg. of I identical in infrared spectrum with the material prepared in (a) above.

Anal. Found. C, 84.37; H, 4.93; N, 10.96.

Infrared spectrum (μ). 2.93 (N—H); 3.28 (C—H); 6.19 (N—H bend and aromatic C=C stretch); 6.56; 6.86; 6.91; 7.57; 7.89; 8.10; 8.48; 8.76; 9.05; and, 11.67, 11.78, 13.12, 13.27, 13.47, and 14.48 (C—H out of plane deformation).

Indolo[2,3-b]carbazole (III). Twenty-two grams of *N,N'*-diphenyl-*m*-phenylenediamine was passed over the 2% platinum-magnesium oxide catalyst during 283 min. Water and hydrogen were added continuously as above while the temperature of the catalyst was maintained at 500°. The reaction product was extracted with methanol leaving a residue which was recrystallized five times from boiling xylene (about 600 ml. for each recrystallization) to give 0.7 g. of III, m.p. 358–360°.

Anal. Calcd. for $C_{18}H_{12}N_2$. C, 84.38; H, 4.69; N, 10.94. Found. C, 84.46; H, 4.99; N, 11.01.

Infrared spectrum (μ). 2.93 (N—H); 3.28 (C—H); 6.08 and 6.19 (N—H bend and aromatic C=C stretch); 6.85; 6.89; 7.56; 7.93; 8.20; 8.65; 9.00; and 11.30, 12.11, 13.01, 13.32, 13.75, and 14.56 (C—H out of plane deformation).

2,3-Benzocarbazole (V). Twenty grams of molten phenyl-2-naphthylamine was vaporized and passed over the platinum-magnesium oxide catalyst during 107 min. at 500–505° while hydrogen at about 170 ml./min. and water at 2.1 g./hr. were fed concurrently. The contents of the receiver were slurried with 300 ml. of hot benzene and filtered to give 3.49 g. of insoluble material, m.p. 344–348°. Concentration of the filtrate provided an additional 0.62 g. of product, m.p. 335–344°. Recrystallization of the combined products from boiling toluene produced glistening white plates, m.p. 347–349°. Warming a 1-g. portion of the product with 5 ml. of acetic anhydride containing a small lump of fused zinc chloride, provided the acetyl derivative, light tan needles from ethanol m.p. 117–118° (lit. m.p. 117° or 123°[14]).

1,2-Benzocarbazole (VII). Twenty grams of phenyl-1-naphthylamine was catalytically dehydrogenated under conditions identical with those used for V above. The benzene solution of the reaction product was treated with anhydrous hydrogen chloride to precipitate 13.56 g. of phenyl-1-naphthylamine hydrochloride and from the filtrate 4.38 g. of VII (m.p. 229–230°) was obtained on evaporation of most of the solvent. Recrystallization from aqueous ethanol provided glistening white plates of the same melting point. The reported value is 227–228°.[15]

Acknowledgment. The authors are indebted to Mr. R. E. Heffelfinger, Mr. R. J. Jakobsen, and Dr. P. W. Davis for the spectral data, and to the Southern Dyestuff Company Division of American-Marietta Company for permission to publish this work conducted under their sponsorship.

COLUMBUS 1, OHIO

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF PENNSYLVANIA]

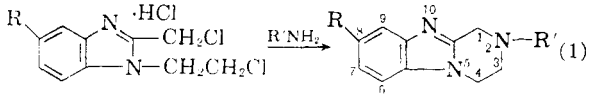
Syntheses of 1,2,3,4-Tetrahydropyrazino[1,2-a]benzimidazoles and 3-Carbethoxy-3-phenyl-1,2,3,4-tetrahydropyrido[1,2-a]benzimidazole

HOWARD MATRICK[1] AND ALLAN R. DAY

Received June 27, 1960

Several 2- and 2,3-substituted 1,2,3,4-tetrahydropyrazino[1,2-a]benzimidazoles have been synthesized. 3-Carbethoxy-3-phenyl-1,2,3,4-tetrahydropyrido-[1,2-a]benzimidazole, a Demerol-like compound, has also been synthesized.

The syntheses of the compounds mentioned in the title were of interest for several reasons. In 1957, Gross and Turian reported the synthesis of a series of benzimidazole derivatives which were active analgesics.[2] The most active compound in the series was 1-(diethylaminoethyl)-2-(4-ethoxybenzyl)-5-nitrobenzimidazole. It occurred to us that the 1,2,3,4-tetrahydropyrazino[1,2-a]benzimidazoles (A), being 1,2-disubstituted benzimidazoles, might have similar properties. Two methods were used for the synthesis of this ring system. The first involved the reaction of a primary amine with 1-(2-chloroethyl)-2-chloromethylbenzimidazole. The other involved the cyclization of 2-bis-(2-chloroethyl)aminomethylbenzimidazole with a base.



(1)

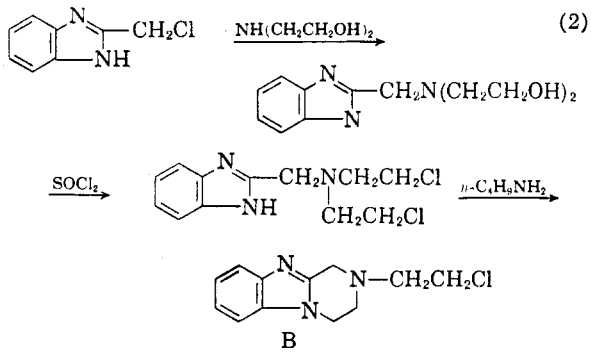
A

R = H, Cl, NO_2, NH_2, $COOC_2H_5$

R' = $C_6H_5CH_2$, $C_6H_5CH_2CH_2$, *n*-C_4H_9

(1) Smith Kline and French Fellow, 1958–59; Eastman Kodak Fellow, 1959–60.

(2) G. Gross and H. Turian, *Experientia*, **13**, 401 (1957).



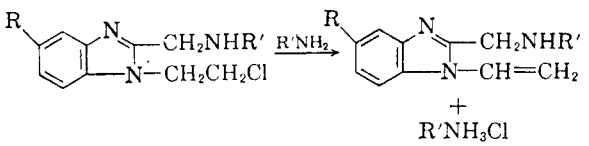
(2)

B

In method 1, two moles of primary amine were used for one mole of 1-(2-chloroethyl)-2-chloromethylbenzimidazole and benzene was the solvent. After standing at room temperature for some time, the reaction mixture was heated in a pressure bottle at 100°. The method has failed in certain cases. For example the use of ammonia and of ethanolamine did not lead to the formation of the expected products.

Method 2 was discovered by accident and has not been thoroughly exploited as yet. An attempt was made to prepare 1-butyl-4-(2-benzimidazolylmethyl)piperazine by the reaction of *n*-butylamine with 2-bis(2-chloroethyl)aminomethylbenzimidazole. Only 2-(2-chloroethyl)-1,2,3,4-tetrahydropyrazino[1,2-a]benzimidazole (B) was isolated from this reaction. This compound had ultraviolet and infrared spectra that were identical with the spectra of A prepared by the first method.

It is theoretically possible that a reaction other than ring closure could take place in these reactions.



While a primary chloride would not be expected to undergo elimination readily, it was necessary to consider this possibility since these vinyl compounds, if formed, would be isomeric with the corresponding 2-alkyl-1,2,3,4-tetrahydropyrazino[1,2-a]benzimidazoles.

1-Vinylbenzimidazole has been prepared previously[3] but no ultraviolet or infrared data were reported. 1-Vinylbenzimidazole has been reported to turn green on standing and to polymerize at 100°. These properties were not noted for the compounds that were prepared in this investigation. The infrared spectra of these compounds failed to show bands which are characteristic of other vinyl compounds such as vinyl benzene. The fact that the same type of structure is obtained from both methods 1 and 2 also suggests that a vinyl group is not present since the pyrazine structure is the only one that can be common to both.

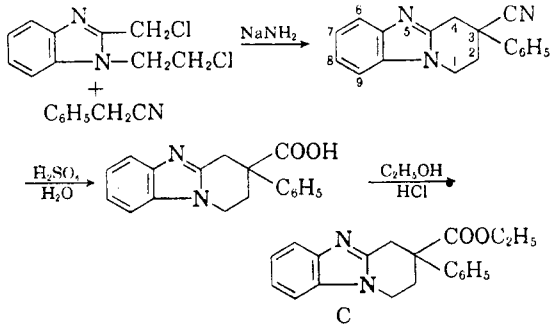
(3) J. Meisenheimer and B. Wieger, *J. prakt. Chem.*, 102, 45 (1921); W. Reppe, *Ann.*, 601, 428 (1956).

Saunders reported the first synthesis of a 1,2,3,4-tetrahydropyrazino[1,2-a]benzimidazole in "trace yields."[4] He isolated 2-carbethoxy-1,2,3,4-tetrahydropyrazino[1,2-a]benzimidazole from the thermal decomposition of *o*-(4-carbethoxypiperazinophenyl)azide.

Schmutz and Kunzle reported the synthesis of several 1,2,3,4-tetrahydropyrazino[1,2-a]benzimidazoles.[5] Their method and compounds prepared did not duplicate the work done in the present investigation.

More recently McManus and Herbst reported the preparation of a tetracyclic and a pentacyclic compound containing the 1,2.3,4-tetrahydropyrazino[1,2-a]benzimidazole nucleus.[6]

At this time it occurred to us that 1-(2-chloroethyl)-2-chloromethylbenzimidazole could also be used for the preparation of a Demerol-like type of compound, namely 3-carbethoxy-3-phenyl-1,2,3,4-tetrahydropyrido[1,2-a]benzimidazole (C). This synthesis was accomplished as follows:



C

EXPERIMENTAL

N-(2-Hydroxyethyl)-2-nitroaniline (I). This compound was prepared from *o*-chloronitrobenzene and ethanolamine, m.p. 69–71°, yield 97%.[7]

N-(2-Hydroxyethyl)-2-nitro-4-chloroaniline (II). 1,4-Dichloro-2-nitrobenzene was the starting material for this preparation, m.p. 70–78°, yield 88%.[7]

N-(2-Hydroxyethyl)-2,4-dinitroaniline (III). 1-Chloro-2,4-dinitrobenzene was used for this preparation, m.p. 91–92°, yield 95%.[7]

N-(2-Hydroxyethyl)-2-nitro-4-carbethoxyaniline (IV). Ethanolamine (12.2 g., 0.2 mole) was heated to 90° and 23 g. (0.1 mole) of ethyl 3-nitro-4-chlorobenzoate was added with stirring over a period of 50 min. The mixture was then heated at 140° for 30 min. After cooling, the oil was stirred with 500 ml. of water until it solidified. The solid was recrystallized from ethanol, m.p. 137–140.5°, yield 66%.

Anal. Calcd. for $C_{11}H_{14}N_2O_5$: C, 51.96; H, 5.55; N, 11.02. Found: C, 52.10; H, 5.73; N, 11.10.

N-(2-Hydroxyethyl)-2-aminoaniline (V) *and N-(2-Hydroxyethyl)-2-amino-4-chloroaniline* (VI) were prepared from the corresponding nitro compounds I and II by catalytic hydrogenation over platinum. The melting points of V and VI were 103–104° and 118–120° respectively.[7]

(4) K. H. Saunders, *J. Chem. Soc.*, 3275 (1955).

(5) J. Schmutz and F. Kunzle, *Helv. Chim. Acta*, 39, 1144 (1956).

(6) J. M. McManus and R. M. Herbst, *J. Org. Chem.*, 29, 1042 (1959).

(7) Dissertation of J. M. Cohen, University of Pennsylvania, 1958.

N-(2-Hydroxyethyl)-2-amino-4-nitroaniline (VII) was prepared from *N*-(2-hydroxyethyl)-2,4-dinitroaniline by reduction with sodium polysulfide,[7] m.p. 131–133°.

N-(2-Hydroxyethyl)-2-amino-4-carbethoxyaniline (VIII). *N*-(2-Hydroxyethyl)-2-nitro-4-carbethoxyaniline (25.4 g., 0.10 mole) in 100 ml. of ethanol was hydrogenated over platinum oxide. After removing the catalyst, the alcohol was distilled *in vacuo*. The dark residue was recrystallized several times from chloroform with the aid of decolorizing carbon; yield 63%, m.p. 123–126°.

Anal. Calcd. for $C_{11}H_{16}N_2O_3$: C, 58.91; H, 7.19; N, 12.49. Found: C, 58.65; H, 7.29; N, 12.58.

1-(2-Hydroxyethyl)-2-hydroxymethylbenzimidazole (IX), *1-(2-hydroxyethyl)-2-hydroxymethyl-5-chlorobenzimidazole* (X) *and 1-(2-hydroxyethyl)-2-hydroxymethyl-5-nitrobenzimidazole* (XI). These compounds were prepared from the corresponding diamines (V, VI, and VII) and glycolic acid.[7] The melting points of IX, X, and XI were 155–160°, 150–151°, and 188–191.5°, respectively.

1-(2-Hydroxyethyl)-2-hydroxymethyl-5-carbethoxybenzimidazole (XII). *N*-(2-Hydroxyethyl)-2-amino-4-carbethoxyaniline (11.2 g., 0.05 mole) and 3.8 g. (0.05 mole) of glycolic acid were heated at 120–130° for 4 hr. The resulting sirup was solidified by treatment with ether. The crude product was recrystallized several times from chloroform; yield 70%, m.p. 166–171°.

Anal. Calcd. for $C_{13}H_{16}N_2O_4$: C, 59.08; H, 6.10; N, 10.60. Found: C, 59.09; H, 6.24; N, 10.57.

1-(2-Chloroethyl)-2-chloromethylbenzimidazole hydrochloride (XIII), *1-(2-chloroethyl)-2-chloromethyl-5-chlorobenzimidazole hydrochloride* (XIV), *and 1-(2-chloroethyl)-2-chloromethyl-5-nitrobenzimidazole hydrochloride* (XV). These compounds were prepared from the corresponding hydroxy compounds (IX, X, and XI) by reaction with thionyl chloride in chloroform solution.[7] The melting points for XIII, XIV, and XV were 174–176°, 189–193°, and 200–205° dec. Compound XIII was first reported in 1957.[8]

1-(2-Chloroethyl)-2-chloromethyl-5-carbethoxybenzimidazole hydrochloride (XVI). 1-(2-Hydroxyethyl)-2-hydroxymethyl-5-carbethoxybenzimidazole (2.64 g., 0.01 mole) was suspended in 30 ml. of chloroform. To this was added dropwise, 10 ml. of thionyl chloride with stirring. The mixture was refluxed for 4 hr., then cooled and ether added until precipitation was complete. The product was removed, washed with ether, and recrystallized from ethanol, yield 75%, m.p. 172–178° dec.

Anal. Calcd. for $C_{13}H_{15}Cl_3N_2$: C, 46.24; H, 4.48; N, 8.30; Cl, 31.50. Found: C, 46.40; H, 4.42; N, 8.26; Cl, 31.26.

2-n-Butyl-1,2,3,4-tetrahydropyrazino[1,2-a]benzimidazole (XVII). 1-(2-Chloroethyl)-2-chloromethylbenzimidazole hydrochloride (5.32 g., 0.02 mole) was added to 75 ml. of benzene in a pressure bottle. The bottle was flushed with nitrogen and 5.92 ml. (0.06 mole) of *n*-butylamine was added. The bottle was stoppered and allowed to stand at room temperature for 44 hr. Then it was heated at 100° for 16 hr. After cooling, the solid was removed by filtration and the filtrate distilled *in vacuo* to obtain a semisolid product. The latter was extracted with ether and petroleum ether (b.p. 30–60°) added. The solution was concentrated and cooled to −20° to obtain a colorless solid, yield 38%, m.p. 92–93.5°.

Anal. Calcd. for $C_{14}H_{19}N_3$: C, 73.32; H, 8.35; N, 18.32. Found: C, 73.52; H, 8.09; N, 18.51.

2-(2-Phenylethyl)-1,2,3,4-tetrahydropyrazino[1,2-a]benzimidazole (XVIII). This compound was prepared by the procedure used for XVII except that 2-phenylethylamine was used in place of butylamine; yield 40%, m.p. 108–111°.

Anal. Calcd. for $C_{18}H_{19}N_3$: C, 77.94; H, 6.90; N, 15.15. Found: C, 77.98; H, 7.11; N, 15.06.

2-n-Butyl-8-chloro-1,2,3,4-tetrahydropyrazino[1,2-a]benzimidazole (XIX). Compound XIX was prepared from XIV and *n*-butylamine by the procedure used for making XVII. The product was recrystallized from diethyl ether, yield 27%, m.p. 127–129°.

Anal. Calcd. for $C_{14}H_{18}ClN_3$: C, 63.75; H, 6.88; N, 15.93; Cl, 13.44. Found: C, 63.56; H, 7.02; N, 16.00; Cl, 13.64.

2-n-Butyl-8-nitro-1,2,3,4-tetrahydropyrazino[1,2-a]benzimidazole (XX). The procedure used for the preparation of compound XVII was used here also, starting from XV and *n*-butylamine, yield 22%, m.p. 106–109°.

Anal. Calcd. for $C_{14}H_{18}N_4O_2$: C, 61.30; H, 6.61; N, 20.43. Found: C, 61.42; H, 6.47; N, 20.41.

2-n-Butyl-8-amino-1,2,3,4-tetrahydropyrazino[1,2-a]benzimidazole (XXI). Compound XX (0.9 g.) was dissolved in 50 ml. of ethanol and hydrogenated over 0.1 g. of platinum oxide. After removing the catalyst, the ethanol was distilled under reduced pressure. It was recrystallized from diethyl ether–petroleum ether (b.p. 30–60°), yield 77%, m.p. 122–123.5°.

Anal. Calcd. for $C_{14}H_{20}N_4$: C, 68.82; H, 8.25; N, 22.93. Found: C, 68.82; H, 8.31; N, 22.75.

2-n-Butyl-8-carbethoxy-1,2,3,4-tetrahydropyrazino[1,2-a]-benzimidazole (XXII). This product was obtained from compound XVI and *n*-butylamine by the procedure used for making XVII; yield 37%, m.p. 128–130°.

Anal. Calcd. for $C_{17}H_{23}N_3O_2$: C, 67.75; H, 7.69; N, 13.94. Found: C, 67.75; H, 7.82; N, 13.91.

2-Benzyl-1,2,3,4-tetrahydropyrazino[1,2-a]benzimidazole (XXIII). Compound XXIII was prepared from XIII and benzylamine by the general procedure, yield 41%, m.p. 124–124.5°.

Anal. Calcd. for $C_{17}H_{17}N_3$: C, 77.53; H, 6.51; N, 15.96. Found: C, 77.35; H, 6.62; N, 16.04.

2-Bis(2-hydroxyethyl)aminomethylbenzimidazole dihydrochloride (XXIV). 2-Chloromethylbenzimidazole[9] (4.2 g., 0.027 mole) and 6 g. (0.057 mole) of diethanolamine were stirred and heated for 4.5 hr. on a steam bath. The mass was dissolved in 150 ml. of hot water and the solution filtered. To the filtrate was added 147.5 ml. of 4% alcoholic picric acid. On cooling a 63% yield of the picrate separated. The picrate was ground with 30 ml. of concd. hydrochloric acid. The mixture was extracted several times with benzene until most of the color was removed. The aqueous phase was diluted with an equal volume of water, heated with decolorizing carbon, filtered, and the filtrate evaporated to dryness. The residue was extracted with ethanol, the solution filtered and the filtrate evaporated to dryness. The residue was washed with a little ether, yield 62%, m.p. 184–186°.[10]

2-Bis(2-chloroethyl)aminomethylbenzimidazole hydrochloride (XXV). 2-Bis-(2-hydroxyethyl)aminomethylbenzimidazole dihydrochloride (3.8 g., 0.018 mole) was suspended in 25 ml. of chloroform and 15 ml. of thionyl chloride added slowly with stirring. After refluxing for 4 hr., the solution was cooled and diethyl ether added until no more hydrochloride precipitated. The product was removed and washed with ether, yield 78%, m.p. 142–147°. It was recrystallized from acetone, yield 45%, m.p. 154–155°.[10]

2-(2-Chloroethyl)-1,2,3,4-tetrahydropyrazino [1,2-a]benzimidazole (XXVI). 2-Bis(2-chloroethyl)aminomethylbenzimidazole hydrochloride (2.32 g., 0.0075 mole) was placed in a pressure bottle with 75 ml. of dry benzene. After adding 2.22 ml. (0.0225 mole) of *n*-butylamine, the flask was flushed with nitrogen, stoppered, and allowed to stand at room temperature for 32 hr. It was then heated for 12 hr. at 100°. After cooling, the mixture was filtered and the precipitate washed with benzene. The filtrate and washings were distilled *in vacuo*. The residual oil was solidified by dissolving it in dry ethanol and distilling the ethanol. It was then recrystallized from diethyl ether–petroleum ether; yield 28%, m.p. 90–93°.

(8) E. Hirschberg, A. Gelhorn, and W. Gump, *Cancer Research*, 17, 904 (1957).

(9) H. Skolnick, J. G. Miller, and A. R. Day, *J. Am. Chem. Soc.*, 65, 1854 (1943).

(10) O. F. Ginsburg *et al.*, *J. Gen. Chem.* (*U.S.S.R.*), 27, 465 (1957).

Anal. Calcd. for $C_{12}H_{14}ClN_3$: C, 61.14; H, 5.99; N, 17.83; Cl, 15.04. Found: C, 61.23; H, 6.21; N, 17.80; Cl, 14.90.

3-Cyano-3-phenyl-1,2,3,4-tetrahydropyrido[1,2-a]benzimidazole (XXVII). Phenylacetonitrile (4.62 ml., 0.04 mole) was dissolved in 50 ml. of dry toluene in a 500-ml. flask which was equipped with a gas inlet tube, powder funnel, and a mechanical stirrer. To this was added, with stirring in a nitrogen atmosphere, 1.6 g. (0.04 mole) of sodamide which had been pulverized under toluene. Excess toluene was used to wash the sodamide into the flask. The powder funnel was immediately replaced with a condenser equipped with a soda-lime tube. Stirring was continued for 15 min., at which time 9.16 g. of 1-(2-chloroethyl)-2-chloromethylbenzimidazole in 125 ml. of dry toluene was added dropwise over a period of 30 min.[11] The mixture was refluxed for 2 hr., cooled, and another 1.6 g. of pulverized sodamide was added. The mixture was then refluxed for 4 hr., filtered hot, and the filtrate cooled overnight. The precipitate was washed with petroleum ether (b.p. 30–60°) and recrystallized from benzene-hexane, yield 17%, m.p. 215–216.5°.

Anal. Calcd. for $C_{18}H_{15}N_3$: C, 79.09; H, 5.53; N, 15.37. Found: C, 79.06; H, 5.66; N, 15.53.

3-Carboxy-3-phenyl-1,2,3,4-tetrahydropyrido-1,2,3,4-tetrahydropyrido[1,2-a]benzimidazole hemihydrate (XXVIII). One gram of 3-cyano-3-phenyl-1,2,3,4-tetrahydropyrido[1,2-a]-benzimidazole was added gradually to a solution of 8 g. of concd. sulfuric acid and 2 g. of water. The solution was heated at 145–150° for 2 hr. The *p*H of the solution was adjusted to about 5 with 40% sodium acetate solution and the solution cooled for 1 hr. The solid so obtained was removed, washed with water, and dried; yield 86%, m.p. 274–276°. It was recrystallized from ethanol-water and dried at 100°/4 mm. for 4 hr., m.p. 285–287° dec.

Anal. Calcd. for $C_{18}H_{16}N_2O_2 \cdot {}^1/_2H_2O$: C, 71.74; H, 5.69; N, 9.30. Found: C, 71.65; H, 5.90; N, 9.46.

3-Carbethoxy-3-phenyl-1,2,3,4-tetrahydropyrido[1,2-a]benzimidazole (XXIX). 3-Carboxy-3-phenyl-1,2,3,4-tetrahydropyrido[1,2-a]benzimidazole hemihydrate (1.6 g., 0.0054 mole) was added to 250 ml. of a saturated solution of hydrogen chloride in dry ethanol. The mixture was allowed to stand for 8 days at room temperature with occasional shaking. When all of the solid had dissolved, the alcohol was removed under reduced pressure. The resulting sirup was dissolved in 50 ml. of dry ethanol and the latter removed by distillation. This was repeated until trituration of the oil with diethyl ether produced a solid. The latter was dissolved in water and the solution neutralized with sodium bicarbonate. The oil which formed, on prolonged trituration with water, changed to a solid. In later experiments seeding with crystals shortened this process. The product was recrystallized from hexane; yield 83%, m.p. 146–147.5°.

Anal. Calcd. for $C_{20}H_{20}N_2O_2$: C, 74.97; H, 6.29; N, 8.75. Found: C, 74.87; H, 6.26; N, 8.72.

The pharmacological properties of the compounds prepared in this investigation are being studied and the data will be reported elsewhere.

PHILADELPHIA 4, PA.

(11) The free base was prepared from 1-(2-chloroethyl)-2-chloromethylbenzimidazole hydrochloride. The latter was dissolved in water, cooled to 0°, and the solution neutralized with sodium bicarbonate solution. After drying in a vacuum desiccator, the product was recrystallized from hexane, m.p. 102–103°.

[CONTRIBUTION FROM THE RESEARCH LABORATORY OF HOFFMAN-LA ROCHE, INC.]

Synthesis of 5-Substituted 3-Isoxazolecarboxylic Acid Hydrazides and Derivatives

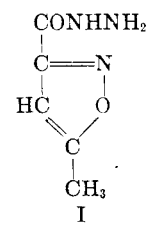
THOMAS S. GARDNER, E. WENIS, AND JOHN LEE

Received July 15, 1960

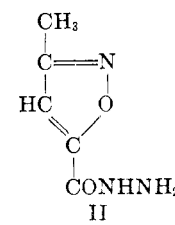
Some 5-substituted 3-isoxazolecarboxylic acid hydrazides have been prepared for investigation of their anti-lepral activity. The 5-methyl, *n*-propyl, and isobutyl compounds showed activity. The 5-methyl compound was superior. Other alkyl residues gave less activity. Aromatic or heterocyclic residues conferred no special activity. Some derivatives and related compounds were prepared.

The development of a reproducible screening procedure for lepraemurium infections in mice by Grunberg and Schnitzer[1] in our chemotherapy laboratories permitted concurrent testing in leprosy of compounds prepared in an anti-tubercular program in progress. 5-Methyl-3-isoxazolecarboxylic acid hydrazide (I),[2] originally found to be inactive in tuberculosis in mice, proved to be active against the lepraemurium infections in mice and rats.

It was therefore thought of interest to examine further hydrazides of this heterocyclic system and some related compounds. The most active compound examined was found to be the initially tested compound (I) which was in the order of ten times the activity of promin in leprosy in both mice and rats. Its position isomer, 3-methyl-5-isoxazolecarboxylic acid hydrazide (II)[3] was inactive.



I



II

In order to determine the effect of isosterism[4] and isomerism, 5-methyl-3-pyrazolecarboxylic acid

(1) E. Grunberg and H. J. Schnitzer, *Ann. N. Y. Acad. Sci.* (*Leprosy*), 54, Art. 1, 107 (1951).

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