[CONTRIBUTION FROM THE RESEARCH DIVISION, BRISTOL LABORATORIES INC.]

Carboxamido Derivatives of the Tetracyclines

BY WILLIAM J. GOTTSTEIN, WILLIAM F. MINOR AND LEE C. CHENEY

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N-(Morpholinomethyl)-tetracycline (VI) has been prepared in a high yield by the interaction of tetracycline (I), morpholine and formaldehyde in *t*-butyl alcohol. Treatment of VI with an aqueous solution of sodium bisulfite and also low-pressure hydrogenolysis of VI with Raney nickel catalyst have regenerated tetracycline. Other substantial evidence that the morpholinomethyl radical is attached to the nitrogen atom of the carboxamido grouping has been presented. The synthesis of N-(dibenzylaminomethyl)-tetracycline (VII), N-(piperidinomethyl)-tetracycline (VIII), N-(pyrolidinomethyl)-tetracycline (IX), N-(morpholinomethyl)-chlorotetracycline, N-(morpholinomethyl)-oxytetracycline and N-(9-xanthyl)-tetracycline (X) have been described.

The variety and steric proximity of the functional groups in the tetracycline family of antibiotics (I, II, III)[1] explain the complex chemical reactions of these *Streptomyces* metabolites and present formidable obstacles in the synthesis of various functional derivatives of particular interest for the study of structure–activity relationships.

I, tetracycline (R_1 and R_2 = H)
II, chlorotetracycline (R_1 = H; R_2 = Cl)
III, oxytetracycline (R_1 = OH; R_2 = H)

The observation that III was converted into 10-benzenesulfonyloxytetracyclinonitrile[2] by treatment with benzenesulfonyl chloride in cold pyridine and that II gave rise to chlortetracyclinonitrile[3] in the presence of *p*-toluenesulfonyl chloride and pyridine has led to a patent[4] claiming the nitriles derived from I, II and III and to a note[5] indicating the generality of the arylsulfonyl halide–pyridine reagent for the conversion of primary amides into nitriles. A report[6] relating to the preparation and structure of 4-*epi*-tetracyclines has described the use of this method for the preparation of benzenesulfonyltetracylinonitrile dimethylformamide solvate and benzenesulfonyl-4-*epi*-tetracyclinonitrile monohydrate; the modification of using methanesulfonyl chloride was introduced for the preparation of 7-chlorotetracyclinonitrile and 7-chloro-4-*epi*-tetracyclinonitrile monohydrate.

The only other reported carboxamido derivatives of the tetracyclines possessing an intact hydronaphthacene skeleton are the anhydrotetracycline derivatives IV and V wherein facile concomitant acid-promoted dehydration at C_{5a}–C_6 has brought about aromatization of ring C. N-Acetonylanhydroöxytetracycline (IV)[2] was prepared by the action of hydrogen chloride on III in cold anhydrous acetone.

IV, (R = —C(CH$_3$)(OH)—CH$_3$; R_1 = OH; R_2 = H; R_3 = H)

V, (R = —C(CH$_3$)$_2$—CH$_3$; R_1 = H; R_2 = H or Cl; R_3 = H or —C(CH$_3$)$_2$—CH$_3$)

More recently Stephens and Lynch[7] disclosed a series of N-*t*-butyl derivatives of anhydrotetracycline (V) produced from either tetracycline amides or nitriles by means of a combination of a Friedel–Crafts alkylation and a Ritter reaction. Experimental details have not been described.

In this Laboratory it has been observed that tetracycline (I)[8] condenses readily with morpholine and formaldehyde in a medium of *t*-butyl alcohol to form a water-soluble, essentially neutral morpholinomethyl derivative (VI) possessing high antimicrobial activity. Experimental conditions are those known to be favorable for effecting a condensation of the Mannich type[9] wherein phenolic ring D would undergo alkylation or, alternatively, an N-alkylation of the class extensively studied by Einhorn[10] involving substitution of the primary carboxamido function on ring A. Other workers[11]

(1) The chemistry of tetracyclines, including tetracycline, chlorotetracycline (Aureomycin) and oxytetracycline (Terramycin) has been presented concisely by P. P. Regna, L. M. Pruess and C. H. Demos in R. E. Kirk and D. F. Othmer's "Encyclopedia of Chemical Technology," Vol. XIII, Interscience Publishers, Inc., New York, N. Y., 1954, pp. 772–810.

(2) F. A. Hochstein, *et al.*, THIS JOURNAL, **75**, 5455 (1953).

(3) C. R. Stephens, *et al.*, *ibid.*, **76**, 3568 (1954).

(4) Chas. Pfizer and Co., Inc., British Patent 766,512 (1957).

(5) C. R. Stephens, E. J. Blanco and F. J. Pilgrim, *ibid.*, **77**, 1701 (1955).

(6) J. R. D. McCormick, *et al.*, *ibid.*, **79**, 2849 (1957).

(7) (a) C. R. Stephens, Abstracts of Papers 129th Meeting American Chemical Society, Dallas, Tex., 1956. p. 18M; (b) J. E. Lynch and C. R. Stephens, "Antibiotics Annual 1955–1956," Medical Encyclopedia, Inc., New York, N. Y., 1956, pp. 466–472.

(8) The trademark of Bristol Laboratories, Inc. for tetracycline phosphate complex is Tetrex ("New and Non-official Drugs," 1958, J. B. Lippincott Co., Philadelphia, Pa., p. 119); the systematic name for tetracycline is 4-dimethylamino-1,4,4a,5,6,11,12a-octahydro-3,6,10,12,12a - pentahydroxy - 6 - methyl - 1,11, - dioxo - 2 - naphthacenecarboxamide (*C. A.*, **47**, 1575s (1953)).

(9) F. F. Blicke in Adams "Organic Reactions," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1942, pp. 303–341.

(10) A. Einhorn, *Ann.*, **343**, 207, 210 (1905); the preparation of N-(piperidinomethyl)-benzamide (p. 233) is especially pertinent.

(11) (a) W. Seidel, A. Soder and F. Lindner, *Munch. med. Wochschr.*, **17**, 661 (1958); (b) F. Lindner, W. Seidel and A. Soder, Union of South Africa patent specification 3169/57.

have recently disclosed the synthesis of morpholinomethyltetracycline hydrochloride and analogs, including pyrrolidinomethyltetracycline which is being marketed in Germany under the name "Reverin." Without any supporting structural evidence these aminomethyltetracyclines are presented as C-alkylation products of the phenolic ring. Prior to the publication of the German work VI had been selected as a representative member of our series for structural elucidation. The following chemical and spectral data are interpreted as definitely proving that these compounds are carboxamido derivatives.

Structure VI was assigned initially to this morpholinomethyl derivative on the basis of spectral data. The infrared absorption curve of compound VI exhibits a splitting of the 6 μ band into 3 peaks at 6.1, 6.2 and 6.3 μ and also shows evidence of a doublet at 6.53 and 6.58 μ characteristic of a monosubstituted amide. This doublet is not seen in the spectrum of tetracycline. The 3 μ region, which shows characteristic OH and NH stretching frequencies, does not appear to be altered with reference to tetracycline. A strong ether band not present in tetracycline is also shown at 9 μ.

Treatment of salicylamide with formaldehyde and morpholine under conditions comparable to those used for the synthesis of VI afforded a model compound, N-(morpholinomethyl)-salicylamide (XI), which gave a deep purple coloration with an aqueous solution of ferric chloride. Hydrogenolysis of XI over Raney nickel led to the isolation of salicylamide. The infrared spectrum of the model compound (XI) shows bands at 6.53–6.58 and 9 μ similar to those of VI. Ultraviolet absorption data are presented in Table I.

TABLE I
ULTRAVIOLET ABSORPTION SPECTRA[a]

Compound	λ_{max}, absorption, mμ	ϵ	ϵshorter/ϵlonger
Tetracycline hydrochloride	366	15352	
	270	16314	1.063
Tetracycline	365	14577	
	268	15599	1.069
N-(Morpholinomethyl)-tetracycline	380	13045	
	270	16143	1.238
N-(9-Xanthyl)-tetracycline	371	8370	
	274	9557	1.142

[a] The solvent used was methanol; the ratio of extinctions of shorter to longer wave lengths has a deviation of ±0.02.

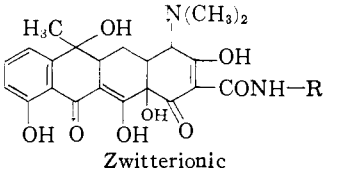
From the table it can be seen that substitution of the amide exhibits a shift from 369 μ of tetracycline to 380 μ for N-(morpholinomethyl)-tetracycline. Further differences are characterized by the values of the extinction coefficients and their ratio for the ϵ shorter/ϵ longer wave lengths.

Convincing chemical evidence has been adduced in support of structure VI. Low-pressure hydrogenation of a methanolic solution of VI in the presence of Raney nickel catalyst proceeded below 50° to give a high yield of 4-methylmorpholine and a crystalline material whose ultraviolet and infrared spectra were identical with those of tetracycline instead of a nuclear methylated tetracycline which would be the expected degradation product in the event that the morpholinomethyl grouping had entered the C_7- or C_9-position.[12] The observation that tetracycline was regenerated quantitatively at room temperature on treatment of VI with aqueous sodium bisulfite served to confirm the structure assigned.

Analogs of VI have been prepared by using a variety of amines in place of morpholine, exemplified by the synthesis of N-(dibenzylaminomethyl)-tetracycline (VII), N-(piperidinomethyl)-tetracycline (VIII), N-(pyrrolidinomethyl)-tetracycline (IX), N-(morpholinomethyl)-chlorotetracycline and N-(morpholinomethyl)-oxytetracycline. These compounds all show bands in the 6.53–6.58 μ region of their infrared spectra. However, in the cases where the morpholino moiety is not present, the ether band at 9 μ is absent, thus eliminating the possibility of O-alkylation.

Reaction of VI with methyl *p*-toluenesulfonate in acetonitrile formed a monoquaternary ammonium salt which has a high antimicrobial activity in contrast to the tetracycline quaternaries reported by Boothe, *et al.*[13]

9-Xanthenol, a well known reagent for the characterization of primary amides,[14] condensed readily with tetracycline to form N-(9-xanthyl)-tetracycline (X) in a fair yield. This reaction with a relatively bulky reagent shows clearly that the carboxamido group in tetracycline is relatively free from steric hindrance in sharp contrast to the other functional groups in the molecule, as can be visualized with the aid of Stuart–Briegleb atom models.



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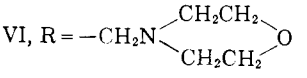

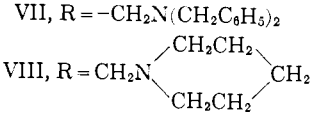

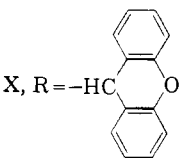

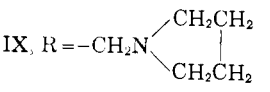

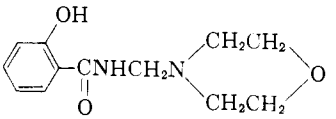

XI

Experimental[15]

N-(Morpholinomethyl)-tetracycline (VI).—Into a suspension of 37.0 g. (0.083 mole) of anhydrous tetracycline

(12) It has been demonstrated that phenolic Mannich bases undergo hydrogenolysis in the presence of Raney nickel catalyst to yield the corresponding nuclear methylated phenols; see R. B. Carlin and H. P. Landerl, THIS JOURNAL, **72**, 2762 (1950); W. B. Wheatley and L. C. Cheney, *ibid.*, **74**, 2940 (1952).

(13) J. H. Boothe, *et al.*, *ibid.*, **80**, 1654 (1958).

(14) R. F. Phillips and B. F. Pitt, *ibid.*, **65**, 1355 (1943).

(15) Melting points are uncorrected. Infrared spectra were determined on a Baird double beam recording spectrophotometer, using potassium bromide pellets. Ultraviolet absorption spectra were taken on a Beckman spectrophotometer equipped with quartz prisms.

(U.S.P.) in 400 ml. of *t*-butyl alcohol were added 8.0 g. (0.091 mole) of freshly-distilled morpholine and 7.3 g. (0.090 mole) of formalin (37% formaldehyde). The mixture was stirred at room temperature for 30 minutes and then heated to boiling (steam-bath) and maintained at this temperature for 15 minutes. The hot solution was filtered by gravity for the removal of a small amount of insoluble material and then cooled promptly to 30°. The pale-yellow amorphous solid was collected by filtration, washed with 35 ml. of *t*-butyl alcohol and air-dried overnight to obtain 41.5 g. (88% yield) of N-(morpholinomethyl)-tetracycline, decomposing over the range 148–154° (after starting to darken at 135° when placed in a bath preheated to 120° and heated at a rate of 2° per minute); water content by the Karl Fischer method, 4.26%. Efforts to obtain a crystalline compound from a number of solvents and solvent combinations were unsuccessful. A sample of the amorphous product was dried for 3 hours at 110° *in vacuo* over phosphorus pentoxide; $[\alpha]^{24}D$ −204.3 (*c* 1, water).

Anal. Calcd. for $C_{27}H_{33}N_3O_9$: C, 59.67; H, 6.13; N, 7.74. Found: C, 59.9; H, 6.25; N, 7.67.

The zwitterion VI is extremely soluble in water; the *p*H of a 1% solution is 6.8. The compound has a biological activity of 590 μg./mg. as determined by the official Food and Drug Administration turbidimetric assay method for tetracycline[16] wherein tetracycline hydrochloride = 1,000 μg./mg.

N-(Dibenzylaminomethyl)-tetracycline (VII).—The same procedure was used as for VI, starting with 37 g. (0.083 mole) of tetracycline, 7.3 g. (0.090 mole) of formalin and 16.5 g. (0.084 mole) of dibenzylamine dissolved in 300 ml. of *t*-butyl alcohol. The weight of N-(dibenzylaminomethyl)-tetracycline obtained was 34.5 g., m.p. 90–95° dec. For analysis the sample was dried *in vacuo* at 80° over phosphorus pentoxide for 2 hr.

Anal. Calcd. for $C_{37}H_{39}N_3O_8$: C, 67.98; H, 6.01; N, 6.32. Found: C, 68.1; H, 6.29; N, 6.34. The biological activity was found to be 500 μg./mg.[16]

N-(Piperidinomethyl)-tetracycline (VIII).—The same procedure was used as for the preparation of VI, starting with 1 g. (0.0023 mole) of tetracycline, 0.23 ml. (0.0024 mole) of piperidine and 0.19 ml. (0.0024 mole) of formalin in 50 ml. of *t*-butyl alcohol. The weight of N-(piperidinomethyl)-tetracycline obtained was 0.78 g., m.p. 150° dec. For analysis the sample was dried *in vacuo* at 60° over phosphorus pentoxide for 1 hour.

Anal. Calcd. for $C_{28}H_{35}N_3O_8$: C, 62.09; H, 6.51. Found: C, 62.2; H, 6.56.

N-(Pyrrolidinomethyl)-tetracycline (IX).—The same procedure was used as for the preparation of VI, starting with 1 g. (0.0023 mole) of tetracycline, 0.19 ml. (0.0023 mole) of pyrrolidine and 0.19 ml. (0.0024 mole) of formalin in 50 ml. of *t*-butyl alcohol. The yellow solid weighed 0.72 g., m.p. 160–165° dec. The sample was dried *in vacuo* over phosphorus pentoxide at 100° for 1 hour. The infrared spectrum of IX and that of pyrrolidinomethyltetracycline prepared by the procedure of Lindner, Seidel and Soder[11b] are identical.

Anal. Calcd. for $C_{27}H_{33}N_3O_8$: C, 61.35; H, 6.29. Found: C, 61.5; H, 6.35.

N-(Morpholinomethyl)-chlorotetracycline.—The same procedure was used as for the preparation of VI, starting with 2.52 g. (0.0053 mole) of chlortetracycline, 0.48 ml. (0.0055 mole) of morpholine and 0.42 ml. (0.0056 mole) of formalin in 100 ml. of *t*-butyl alcohol. The yield was 2.8 g., m.p. 155° dec. For analysis the sample was dried *in vacuo* over phosphorus pentoxide overnight at 50°.

Anal. Calcd. for $C_{27}H_{32}ClN_3O_9$: C, 56.10; H, 5.58. Found: C, 56.2; H, 6.25.

N-(Morpholinomethyl)-oxytetracycline.—The same procedure was used as for the preparation of VI, starting with 2.46 g. (0.0054 mole) of oxytetracycline, 0.48 g. (0.0055 mole) of morpholine and 0.42 ml. (0.0056 mole) of formalin in 100 ml. of *t*-butyl alcohol. The yield was 1.4 g., m.p. 155° dec. For analysis the sample was dried at 60° *in vacuo* over phosphorus pentoxide for 1 hour.

Anal. Calcd. for $C_{27}H_{33}N_3O_{10}$: C, 57.95; H, 5.94. Found: C, 57.4; H, 6.46.

N-(Morpholinomethyl)-tetracycline Methyl *p*-Toluenesulfonate.—To a suspension of 54.4 g. (0.10 mole) of N-(morpholinomethyl)-tetracycline (VI) in 500 ml. of acetonitrile was added 20.4 g. (0.11 mole) of methyl *p*-toluenesulfonate (Eastman). The mixture was heated to boiling and maintained at this temperature under reflux for 5 minutes, then filtered and the filtrate stored overnight at 10°. The amorphous solid was collected by filtration and air-dried to obtain 30.1 g. (42% yield) of pale yellow solid, m.p. 160–165° dec. with shrinking and discoloration above 150°. The compound had a biological assay of 525 μg./mg.[16] For analysis this material was dried *in vacuo* at 60° over phosphorus pentoxide for 1 hour.

Anal. Calcd. for $C_{35}H_{43}N_3O_{12}S$: C, 57.45; H, 5.92. Found: C, 57.7; H, 6.04.

Hydrogenolysis of N-(Morpholinomethyl)-tetracycline (VI). (A) Isolation of 4-Methylmorpholine.—To a solution of 50.0 g. (0.092 mole) of N-(morpholinomethyl)-tetracycline in 175 ml. of methanol was added 25 g. of methanol-washed Raney nickel catalyst (commercial). The suspension was shaken in a Parr low-pressure hydrogenator at 45° under an initial gauge pressure of 50 lb./sq. in. for 4 hours, during which time the hydrogen uptake was approximately 0.09 mole. Following removal of catalyst by filtration, the filtrate was steam distilled until the fresh distillate was no longer basic. Acidification of the distillate with hydrochloric acid followed by its evaporation to dryness on the steam-bath left a residue of 11.1 g. (88% yield) of 4-methylmorpholine hydrochloride, m.p. 201–203°. The infrared spectrum of this material was identical with the spectrum obtained from an authentic specimen of 4-methylmorpholine hydrochloride.[17]

(B) Isolation of Tetracycline.—To a solution of 25 g. (0.046 mole) of N-(morpholinomethyl)-tetracycline in 150 ml. of methanol was added 24 g. of methanol-washed Raney nickel catalyst (commercial) and the mixture was hydrogenated as described under (A). After removal of the catalyst by filtration and distillation of the methanol under reduced pressure (water aspirator), the residue crystallized on treatment with 100 ml. of water. The product was collected by filtration and recrystallized by dissolving it in water made acidic (*p*H 1.4) with hydrochloric acid, followed by the gradual addition of ammonia until *p*H 4 was reached. The dried yellow crystals, m.p. 174–176° dec., weighed 9.0 g. (43% yield). The ultraviolet and infrared spectra were identical with those of authentic tetracycline.

Regeneration of Tetracycline from N-(Morpholinomethyl)-tetracycline (VI) Using Sodium Bisulfite.—To a solution of 10.0 g. (0.018 mole) of N-(morpholinomethyl)-tetracycline in 100 ml. of water was added 4.0 g. of sodium bisulfite. The solution was stirred for 0.5 hour, filtered, and the precipitate was dried overnight at room temperature over phosphorus pentoxide to give 8.0 g. (96% yield) of a yellow crystalline solid. The infrared spectrum was found to be identical with that of authentic tetracycline.

N-(Morpholinomethyl)-salicylamide (XI).—A mixture of 68.5 g. (0.5 mole) of salicylamide, 250 ml. of methanol, 44.5 g. (0.51 mole) of morpholine and 47 g. (0.58 mole) of formalin (37% formaldehyde) was boiled under reflux for 15 minutes and then concentrated under reduced pressure to approximately one-third of the original volume. The solid residue was stirred with 100 ml. of water and collected by filtration. The product was dissolved in 200 ml. of boiling ethyl acetate, treated with charcoal (Darco G-60) and filtered. Dilution of the filtrate with 400 ml. of cyclohexane and cooling gave 12 g. (10% yield) of crystals, m.p. 124–125°, which were dried *in vacuo* over phosphorus pentoxide.

Anal. Calcd. for $C_{12}H_{16}N_2O_3$: C, 60.98; H, 6.82. Found: C, 61.2; H, 6.99.

The solubility of this compound in water is less than 1% at room temperature, but it is quite soluble in very dilute hydrochloric acid (*p*H below 4.7). A dilute solution of XI turned purple on treatment with ferric chloride reagent. The infrared absorption spectrum shows bands at 6.53, 6.58 and 9 μ characteristic of a monosubstituted amide function and an ether linkage, respectively, as observed in the infrared spectrum of N-(morpholinomethyl)-tetracycline (VI).

Regeneration of Salicylamide from N-(Morpholinomethyl)-salicylamide (XI).—A solution of 4.0 g. (0.017 mole) of

(16) Federal Register, pp. 9291–9292, Nov. 28, 1956.

(17) L. Knorr, *Ber.* **22**, 2091 (1899).

XI in 100 ml. of methanol was hydrogenated over Raney nickel for 2 hours at room temperature under an initial gauge reading of 50 lb./sq. in. The catalyst was filtered and the methanol was evaporated. The white crystalline residue was recrystallized from 20 ml. of boiling water to give 1.2 g. of a solid (51% yield), m.p. 140°, which did not depress the melting point of authentic salicylamide. The infrared spectrum was identical with the spectrum obtained from salicylamide.

N-(9-Xanthyl)-tetracycline (X).—To 500 ml. of glacial acetic acid contained in a 1-liter erlenmeyer flask was added slowly with stirring 60 g. (0.135 mole) of anhydrous tetracycline. After nearly all of the tetracycline had dissolved 29.8 g. (0.150 mole) of 9-xanthenol (xanthydrol, Eastman) was added and the mixture was heated and stirred on the steam-bath at 45–50° for 15–20 minutes. The resulting solution was poured into 2 liters of water to form a milky precipitate which was extracted with 2 liters of ethyl acetate in 3 portions. The combined extracts were washed with 500 ml. of water. The organic layer was concentrated under reduced pressure on the steam-bath to a volume of approximately 400 ml. Dilution with 500 ml. of methanol and chilling caused 50.2 g. of product to crystallize. Recrystallization was accomplished by dissolving the material in 300 ml. of warm ethyl acetate and diluting the solution with 300 ml. of methanol. After drying for two days *in vacuo* over phosphorus pentoxide, the yellow crystals weighed 36.9 g. (40% yield), m.p. 178–180° dec. (with previous darkening and shrinking commencing at about 154° when the temperature was raised 3° per minute). For analysis a sample was dried *in vacuo* at 110° over phosphorus pentoxide for two hours.

Anal. Calcd. for $C_{35}H_{32}N_2O_9$: C, 67.30; H, 5.17; N, 4.49. Found: C, 67.4; H, 4.86; N, 4.45.

Because the solubility of X in water is less than 0.1 mg./ml., a suspension for bioassay was prepared by weighing 100 mg. of a micronized sample into 50 ml. of distilled water, adding 6 drops of Tween 40 and 6 drops of acetone and finally diluting to a volume of 100 ml. with water. The *in vitro* biological activity is about 315 μg./mg.[16] As in the infrared spectrum of VI, the 6 μ infrared band for X is split into 3 peaks at 6.1, 6.2 and 6.3 μ and shows a doublet at 6.53 and 6.58 μ. There is no alteration of the 3 μ region. The ultraviolet absorption spectrum is reported in Table I.

Acknowledgments.—We are indebted to R. M. Downing for the microanalyses, to Professor John C. Sheehan for interpretation of the spectral data and to Dr. F. M. Palermiti and D. L. Evans for the spectral data.

SYRACUSE, N. Y.

[CONTRIBUTION FROM THE DEPARTMENT OF PHARMACEUTICAL CHEMISTRY, UNIVERSITY OF WISCONSIN]

The Quasi-Favorskii Rearrangement. I. The Preparation of Demerol and β-Pethidine

BY EDWARD E. SMISSMAN AND GILBERT HITE

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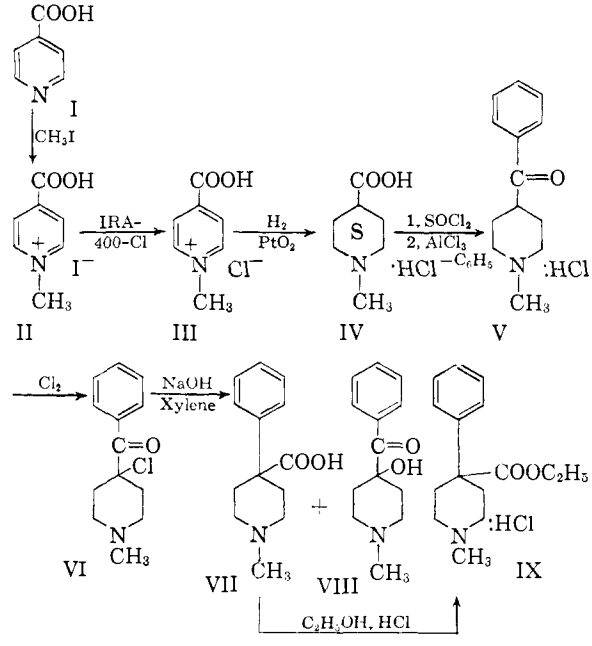
The use of the alkaline rearrangement of α-haloketones in the preparation of two analgesics, Demerol (ethyl 1-methyl-4-phenyl-4-piperidinecarboxylate, IX) and β-Pethidine (ethyl 1-methyl-3-piperidinecarboxylate, X) is reported. This constitutes a novel synthesis for analogs of Demerol-type compounds.

In 1939, Tchoubar and Sackur[1] reported the base-catalyzed rearrangement of α-chlorocyclohexyl phenyl ketone to 1-phenyl-cyclohexanecarboxylic acid. Later Stevens and Farkas[2] investigated the conditions for this reaction and were able to modify the procedure to secure higher yields of the acid.

Since the mechanism of the alkaline rearrangement of α-haloketones having no α-hydrogens has not been elucidated, and because the above rearrangement would give an excellent method for the preparation of Demerol-type compounds, it was decided to synthesize Demerol by a modification of the Favorskii rearrangement.[3] Isonicotinic acid (I) was methylated using methyl iodide, and the resulting methiodide II was converted to the methochloride III with Amberlite IRA-400 (chloride) resin. This compound was then reduced to 1-methyl-4-piperidinecarboxylic acid hydrochloride (IV) which was converted to the acid chloride hydrochloride by allowing it to react with thionyl chloride. The acid chloride hydrochloride was then condensed with benzene under Friedel–Crafts conditions to give 1-methyl-4-benzoylpiperidine hydrochloride (V). Chlorination of the ketone V gave the mono-chloroketone hydrochloride VI in excellent yields. When subjected to alkaline treatment the products obtained were 1-methyl-4-phenyl-4-piperidinecarboxylic acid (VII)



and 1-methyl-4-hydroxy-4-benzoylpiperidine (VIII). Esterification of VII gave the desired

(1) B. Tchoubar and O. Sackur, *Compt. rend.*, **208**, 1020 (1939).

(2) C. L. Stevens and E. Farkas, THIS JOURNAL, **74**, 5352 (1952).

(3) Excellent general papers on the Favorskii reaction: R. Jacquier, *Bull. soc. chim.*, D35 (1950) and R. B. Loftfield, THIS JOURNAL, **73**, 4707 (1951).