treated with activated charcoal. After filtration, the solvent was removed under reduced pressure and the slowly solidifying residue was recrystallized once from benzene–petroleum ether (b.p. 64–69°) and once from benzene–petroleum ether mixture (b.p. 64–69° and b.p. 35–40°) to furnish 1.15 g. (53.8%) of sturdy colorless needles, m.p. 118.5–120°. Recrystallization from ethanol–water gave needles, m.p. 119.5–120.5°. Mixture melting point with a sample prepared according to procedure A showed no depression. The infrared spectra (KBr disk) of the two samples were identical.

3-Benzoylanthranil (3d). A. From 2-Phenylisatogen (1d).—The anthranil **3d** was prepared by isomerization of **1d**[43] in methanol–sulfuric acid at *ca.* 100°[11,44] or in refluxing ethanol–sulfuric acid as described by Jones.[45] Purification and separation from unchanged **1d** was most readily achieved by chromatography on alumina (100 g./g. of crude **3d**; elution with 2:1 and 4:1 benzene–petroleum ether, b.p. 64–69°) as described by Jones.[45] Recrystallization from petroleum ether (b.p. 64–69°, 25 ml./g.) or methanol–water gave long colorless needles, m.p. 95.5–96.0°, lit.[11] m.p. 94°. An infrared spectrum[39a] of **3d** (KBr disk) showed absorption maxima at 1647 (s, C=O), 1623 (m), 1597 (m), 1575 (m), 1553 (m), 1451 (s), 1427 (m), 1399 (w), 1346 (w), 1323 (m), 1311 (w), 1289 (s), 1236 (s, br), 1189 (m), 1182 (m), 1161 (m), 1142 (w), 1074 (vw, br), 1028 (vw), 1002 (vw), 977 (vw), 934 (m), 907 (vw), 889 (s), 795 (vw, br), 769 (m), 763 (m), 752 (s), 712 (m), 694 (s), and 682 cm.$^{-1}$ (m). In a Nujol mull and in chloroform solution the carbonyl band was at 1642[39b] and 1650[39c] cm.$^{-1}$, respectively. The ultraviolet spectrum[38b,40a] in ethanol showed λ_{max} (log ϵ) at 258 (4.07) (sh) and 352 mμ (4.03).[46] The spectrum was unchanged in acidified or basified ethanol solution (apparent pH ~1 and ~11, respectively). A solution of **3d** in ethanol–water did not liberate iodine from a potassium iodide aqueous alcohol solution acidified with sulfuric acid. A similar result was obtained with the solvent system described by Horner and Jürgens.[22b] The colorless needles of **3d** acquired a greenish tint when left in the air and light. A similar color change was most pronounced when a KBr disk of **3d** was irradiated with a 100-w. mercury-vapor lamp for 5 hr.; however, no change in the infrared spectrum was detected. The anthranil may be stored in a tightly stoppered container in the dark without apparent decomposition. In fact, a *ca.* 19-year-old sample of **3d** (slightly contaminated with **1d**) prepared by Dr. E. Caspar[47] had the m.p. 91–94° while an analytical sample of the isoisatogen,[11] prepared by repeated recrystallization from methanol, had the m.p. 95°.

Anal.[38b] Calcd. for $C_{14}H_9NO_2$: C, 75.33; H, 4.07; N, 6.27; mol. wt., 223. Found: C, 75.42, 75.32; H, 4.11, 4.23; N, 6.36, 6.25; mol. wt., 237 (Rast, camphor).

B. From Anthroxanic Acid Chloride (8).—To a stirred solution of phenylmagnesium bromide (5.80 mmoles) in 25 ml. of ether was added 0.570 g. (3.11 mmoles) of anhydrous cadmium chloride. After 25 min. a Michler ketone test[48] for the presence of Grignard reagent was negative. A solution of 0.997 g. (5.49 mmoles) of anthroxanic acid chloride (**8**)[28] in 20 ml. of ether was added during 5 min. After the solution had been stirred at room temperature for 30 min., the ether was replaced during distillation by 30 ml. of anhydrous benzene, and the reaction mixture was maintained at reflux temperature for 1 hr. After the solution had cooled to room temperature, 75 ml. of ether was added, and the reaction mixture was treated with 150 ml. of 20% ammonium chloride solution. The separated aqueous layer was extracted with three 50-ml. portions of ether. The combined ether extracts were subjected to steam distillation for 10 min., and the pot residue was extracted with three 25-ml portions of ether. The combined ether extracts were washed with saturated sodium bicarbonate solution and with water. The dried (Drierite) ether solution was evaporated under reduced pressure and the residue was recrystallized from methanol–water to furnish 0.385 g. (31.4%) of 3-benzoylanthranil (**3d**) as light yellow needles, m.p. 91–93°. The methanol–water filtrate was worked up to afford an oil which, after chromatography on alumina, gave an additional 0.111 g. (9.1%) of **3d**. Recrystallization from methanol–water furnished nearly colorless needles, m.p. 94–95°, undepressed on admixture with an authentic sample of **3d** prepared from **1d**. The infrared spectrum (KBr disk) was identical with that of the authentic sample.

Attempted Reaction of 3-Benzoylanthranil (3d) with Diphenylcadmium.—With 1 equiv. of diphenylcadmium, **3d** was recovered (85%) after 95 min. in benzene at reflux temperature. Reaction did occur when 11 equiv. of diphenylcadmium were used with a reaction time of 1 hr. in benzene at reflux temperature. However, neither **3d** nor **7** could be isolated from the oily reaction product. A small amount of a solid, m.p. 132–133°, was isolated but not identified.

(43) (a) F. Kröhnke and M. Meyer-Delius, *Ber.*, **84**, 932 (1951); (b) F. Kröhnke and I. Vogt, *ibid.*, **85**, 376 (1952).

(44) B. Hegedüs, Dissertation, University of Basel, 1939, p. 30. We thank Dr. Hegedüs for kindly providing a copy of his dissertation.

(45) See ref. 17e, p. 114.

(46) A subsequent determination[30] of the ultraviolet spectrum[40b] showed $\lambda_{max}^{C_2H_5OH}$ (log ϵ) at 218 (3.85) (sh), 261 (3.95), 293 (3.78) (sh), 308 (3.69) (sh), and 354 mμ (4.00).

(47) A number of original samples of nitrogen heterocycles prepared by Professor P. Ruggli and co-workers at the University of Basel were kindly furnished by Professors T. Reichstein and H. Dahn.

(48) A. I. Vogel, "Practical Organic Chemistry," 3rd Ed., Longmans, Green and Co., London, 1957, p. 241.

Indole Alkaloids. III.[1] Oxidation of Secondary Alcohols to Ketones

J. DONALD ALBRIGHT AND LEON GOLDMAN

Organic Chemical Research Section, Lederle Laboratories, A Division of American Cyanamid Company, Pearl River, New York

Received November 13, 1964

Oxidation of yohimbine, methyl reserpate, 16α-methylyohimban-17α-ol, and α-yohimbine with N,N'-dicyclohexylcarbodiimide, orthophosphoric acid, and dimethyl sulfoxide gives the corresponding ketones in 60–80% yields. β-Yohimbine O-*p*-toluenesulfonate is oxidized with dimethyl sulfoxide and tripropylamine to give 25% of yohimban-17-one, but yohimbine O-*p*-toluenesulfonate yields apoyohimbine. Acid hydrolysis of yohimbinone affords yohimban-17-one, whereas base hydrolysis cleaves the E ring with formation of diacid **4**.

Methods for oxidation of a secondary hydroxyl group in indole alkaloids to a ketone are severely limited owing to the sensitivity of the indole moiety to oxidation. The various oxidizing agents involving chromium trioxide, so successful in other fields, are of limited value. The only consistently successful method for oxidation of a hydroxyl group in an indole alkaloid is the modified Oppenauer oxidation.[2] Many variations in the conditions of the Oppenauer oxidation as applied to alkaloids have been developed[3,4]; however, in many

(1) (a) Paper I: J. D. Albright, L. A. Mitscher, and L. Goldman, *J. Org. Chem.*, **28**, 38 (1963). (b) Paper II: L. A. Mitscher, J. K. Paul, and L. Goldman, *Experientia*, **19**, 195 (1963).

(2) (a) B. Witkop, *Ann.*, **554**, 83 (1943); (b) J. Jost, *Helv. Chim. Acta*, **32**, 1297 (1949); (c) Z. J. Vejdělek and K. Macek, *Collection Czech. Chem. Commun.*, **24**, 2493 (1959); (d) R. C. Elderfield, A. E. Hydorn, E. Schenker, and K. K. Wyckoff, *J. Org. Chem.*, **24**, 1296 (1959); (e) A. Le Hir, M.-M. Janot, and R. Goutarel, *Bull. soc. chim. France*, 1027 (1953); (f) S. Kimoto, M. Okamoto, and H. Kondo, *Chem. Pharm. Bull.* (Tokyo), **7**, 650 (1959).

(3) *Cf.* R. B. Woodward, N. L. Wendler, and F. J. Brutschy, *J. Am. Chem. Soc.*, **67**, 1425 (1945); E. W. Warnhoff and P. Reynolds-Warnhoff, *J. Org. Chem.*, **28**, 1431 (1963), and references contained therein.

(4) M.-M. Janot, R. Goutarel, E. W. Warnhoff, and A. Le Hir, *Bull. soc. chim. France*, 637 (1961).

cases yields are only moderate. In addition the Oppenauer oxidation of hydroxy esters such as yohimbine (1) and α-yohimbine (5) which should lead to β-keto esters[2e,f] gives, in general, the decarboxylated product. Special mild conditions have recently been developed for oxidation of yohimbine to the β-keto ester yohimbinone (2) in 51% yield.[4]

Our interest in mild oxidative conditions for the conversion of hydroxyl groups in indole alkaloids to carbonyl derivatives led us to study the oxidation of hydroxy alkaloids with N,N′-dicyclohexylcarbodiimide (DCC), orthophosphoric acid, and dimethyl sulfoxide (DMSO). This procedure has recently been described for the oxidation of certain alcohols[5] and we have found this method to be a mild, convenient oxidative procedure applicable to indole alkaloids. Thus, oxidation of yohimbine under these conditions gave yohimbinone (methyl 17-oxoyohimban-16α-carboxylate) in over 80% yield while oxidation of methyl reserpate and 16α-methylyohimban-17α-ol[6] gave 60% of methyl ketoreserpate[7] and 61% of 16α-methylyohimban-17-one,[2d] respectively. The previously undescribed methyl 17-hydroxyalloyohimb-16-ene-16-carboxylate (α-yohimbinone, 6) was obtained in 52% yield from α-yohimbine. In contrast to yohimbinone which is nonenolic, 6 is completely enolic.[8] There was no carbonyl absorption above 1680 cm.$^{-1}$ in the infrared spectrum and the p.m.r. spectrum showed a sharp singlet at τ −2.40 (enolic OH) which disappeared on addition of deuterated methanol.

Although the oxidation of alcohols with orthophosphoric acid, DCC, and DMSO is somewhat similar to the Kornblum oxidation,[9] the differences are readily apparent on comparison of oxidation experiments with yohimbine O-*p*-toluenesulfonate (8)[1a] and β-yohimbine O-*p*-toluenesulfonate (7).[1a] As anticipated, β-yohimbine O-*p*-toluenesulfonate (equatorial sulfonate ester), on heating with tripropylamine in DMSO, gave a 25% yield of yohimban-17-one, whereas yohimbine O-*p*-toluenesulfonate underwent *trans* diaxial elimination of the elements of *p*-toluenesulfonic acid to yield the α,β-unsaturated ester apoyohimbine (9). With triethylamine as the base, a lower temperature prevailed and β-yohimbine O-*p*-toluenesulfonate was recovered unchanged.

Since the oxidation of yohimbine to yohimbinone proceeded in excellent yield with orthophosphoric acid, DCC, and DMSO, oxidation followed by hydrolysis and decarboxylation should provide an improved method for the preparation of yohimban-17-one (3). Conversion of yohimbinone (2) to ketone 3 with potassium hydroxide in ethanol has been reported,[2f] although no yield was given. In our hands hydrolysis of 2 with potassium hydroxide in ethanol gave only trace amounts (1.4%) of yohimban-17-one. The main product (78%) was the diacid 4 resulting from cleavage of the E ring. Electrometric titration of the diacid with base indicated pK_a values of 4.70 and 7.90. Attack of hydroxide ion at the 17-ketone function of 2, rather than on the ester group, with opening of the E ring (reverse Dieckmann) readily rationalizes the formation of the diacid.

Other conditions for the hydrolysis of yohimbinone (2) were studied. Hydrolysis with aqueous acetic acid or trichloroacetic acid were largely unsuccessful, although some conversion to yohimban-17-one was indicated from the infrared spectrum of the yohimbinone recovered. Hydrolysis with aqueous acetic–sulfuric acid or a mixture of aqueous hydrochloric–acetic acid afforded yohimban-17-one. The yield with the latter reagent was 95%. Thus oxidation of yohimbine (1) to yohimbinone (2) followed by hydrolysis and decarboxylation constitutes a superior method for preparation of yohimban-17-one (3).

From the results reported it is apparent that the oxidation of alcohols with orthophosphoric acid, DCC, and DMSO should find wide application in the alkaloid field.

Experimental

Unless otherwise noted all melting points were taken in sealed capillaries which were inserted in a Mel-Temp apparatus at about 10–40° below the melting point and are uncorrected. Samples for analysis were dried *in vacuo* over phosphorus pent-

(5) K. E. Pfitzner and J. G. Moffatt, *J. Am. Chem. Soc.*, **85**, 3027 (1963).

(6) This compound was incompletely assigned the structure 16-methylyohimbol by P. Karrer and R. Saemann [*Helv. Chim. Acta*, **35**, 1932 (1952)]. It is obvious from its method of preparation that the full designation is 16α-methylyohimban-17α-ol.

(7) M. M. Robison, W. G. Pierson, R. A. Lucas, I. Hsu, and R. L. Dziemian [*J. Org. Chem.*, **28**, 768 (1963)] have prepared methyl ketoreserpate from reaction of methyl reserpate *p*-bromobenzenesulfonate with dimethyl sulfoxide and triethylamine.

(8) E. Wenkert and B. G. Jackson [*J. Am. Chem. Soc.*, **81**, 5601 (1959)] have ascribed the nonenolic properties of yohimbinone (2) to the steric interactions (*peri* effect) of the C-14 hydrogen atoms and the methoxycarbonyl group in the hydrogen-bonded enol.

(9) N. Kornblum, W. J. Jones, and G. J. Anderson, *ibid.*, **81**, 4113 (1959).

oxide at 100° for 18–24 hr. Ultraviolet absorption spectra were measured on a Cary recording spectrophotometer. Infrared spectra were determined on a Perkin-Elmer spectrophotometer (Model 21). P.m.r. spectra were determined with a Varian Model A-60 spectrometer in deuterated dimethyl sulfoxide or deuteriochloroform with tetramethylsilane as internal standard. The dimethyl sulfoxide for the oxidation studies was dried over Molecular Sieves (type 4A, Fisher).

Yohimbinone (2).—To a solution of 28.32 g. (0.080 mole) of yohimbine (1) and 49.04 g. (0.24 mole) of DCC in 120 ml. of dry dimethyl sulfoxide was added 12.0 g. (0.12 mole) of crystalline orthophosphoric acid. When shaken the mixture became hot and was cooled. The mixture was allowed to stand for 17 hr. at room temperature and was poured into 350 ml. of methanol–water (3:2). After standing at room temperature for 30 min. the solid was removed by filtration and washed with aqueous methanol and with aqueous acetic acid. The filtrate was chilled, made basic with concentrated ammonium hydroxide, and diluted with water. Chilling and filtering gave a yellow solid which was washed with water and triturated with ether–methanol (1:1) to give 10.0 g. of product. The basic filtrate was extracted with dichloromethane; the extracts were washed with water and concentrated *in vacuo*. The residue and the 10.0 g. of crude product were combined and dissolved in dichloromethane; the solution was filtered through a column of 40 g. of Florisil®. Elution with dichloromethane (*ca.* 1 l.) and concentration *in vacuo* gave a yellow-orange solid. Trituration with ether–methanol gave, after reworking the mother liquors, 8.65 g. (30%) of 2, m.p. 243–245° dec. The original filter cake (N,N′-dicyclohexylurea plus phosphate salt of product) was extracted alternately with 50% aqueous acetic acid and aqueous methanol until no more product remained in the filter cake. The filtrate was diluted with water, chilled, and made basic with concentrated ammonium hydroxide to give 13.2 g. (47%) of 2 as pale yellow crystals, m.p. 250–254° dec., lit.[4] m.p. 243–249°.

A simplified and more satisfactory work-up procedure entails diluting the original reaction mixture with dichloromethane and filtering off the precipitated solids. The product remains in the filter cake as the phosphate salt and is extracted from the N,N′-dicyclohexylurea with hot acetic acid–water (1:2). Basification of the chilled extract with concentrated ammonium hydroxide, filtration, and trituration of the solid with 3A alcohol gives 2. Yields of over 80% have been obtained by this procedure.

Methyl Ketoreserpate.—Oxidation of 8.29 g. (0.020 mole) of methyl reserpate with 12.26 g. (0.060 mole) of DCC, 1.28 g. (0.013 mole) of orthophosphoric acid, and 25 ml. of dimethyl sulfoxide at 55–60° for 19 hr. gave on work-up 4.95 g. (60%) of pale yellow crystals, m.p. 226–230°. Recrystallization from 95% ethanol and from absolute ethanol gave white crystals: m.p. 237–239°, $[\alpha]^{25}D$ −24° (*c* 1.0, $CHCl_3$); lit.[7] m.p. 241–242° dec., $[\alpha]^{25}D$ −17°.

16α-Methylyohimban-17-one.—Oxidation of 3.1 g. (0.010 mole) of 16α-methylyohimban-17α-ol with 6.13 g. (0.030 mole) of DCC, 1.47 g. (0.015 mole) of orthophosphoric acid, and 20 ml. of dimethyl sulfoxide for 26 hr. at room temperature gave on work-up 1.90 g. (61%) of off-white crystals, m.p. 316–319° dec. Recrystallization from acetone–ethanol gave white needles, m.p. 321–323° dec., lit.[2d] m.p. 293° dec.

Methyl 17-Hydroxyalloyohimb-16-ene-16-carboxylate (6).—A mixture of 14.16 g. (0.040 mole) of α-yohimbine (5), 24.56 g. (0.120 mole) of DCC, 5.88 g. (0.060) mole) of crystalline orthophosphoric acid, and 70 ml. of dimethyl sulfoxide was stirred (heat was liberated and a solid separated) and allowed to stand at room temperature for 22 hr. The mixture was poured into 60 ml. of 50% aqueous acetic acid. After standing for 30 min. the mixture was filtered and the precipitate was washed with three 20-ml. portions of 50% aqueous acetic acid and with two 25-ml. portions of 50% aqueous acetic acid. The filtrate was chilled in an ice bath, 50 g. of ice was added, and the mixture was brought to pH 7 with concentrated ammonium hydroxide. The mixture was chilled and filtered; the solid was washed thoroughly with water. The partially dried solid was dissolved in methanol–dichloromethane and concentrated *in vacuo*. The residue was dissolved in dichloromethane and filtered through a column of 50 g. of Florisil®. Elution with dichloromethane (1300 ml.) and concentration *in vacuo* gave a yellow glass which was dried in a vacuum oven to give 11.4 g. of crude product.

From a reaction run on 0.020 mole of 5 there was obtained 3.65 g. (52%) of 6, m.p. 179–183° dec. Several recrystallizations from ethanol gave 6 as pale yellow crystals: m.p. 185–188°; $[\alpha]^{25}D$ −36° (*c* 1.0 pyridine); ν_{max}^{KBr} 3367 (s), 1642 (s), and 1608 $cm.^{-1}$; $\lambda_{max}^{CH_3OH}$ 224 mμ (ε 38,100), 264 (12,700), 282 sh (9200), and 289 (6700); $\lambda_{max}^{0.1NNaOH}$ 215 mμ (ε 57,400) and 283 mμ (ε 23, 200).

Anal. Calcd. for $C_{21}H_{24}N_2O_3$: C, 71.6; H, 6.86; N, 7.95. Found: C, 71.3; H, 7.02; N, 7.96.

Yohimbine O-*p*-Toluenesulfonate (8).—To a mixture of 10.6 g. (0.030 mole) of yohimbine in 50 ml. of ice-cold dry pyridine was added 15.5 g. (0.090 mole) of *p*-toluenesulfonyl chloride. On standing at room temperature for 17 hr. solid had separated, and 30 ml. of dry chloroform was added. After standing for an additional 48 hr. the mixture was filtered and the precipitate was washed with chloroform. The precipitate was mixed with 200 ml. of chloroform and 100 ml. of water and the mixture was made basic with ammonium hydroxide. After stirring for several hours the chloroform layer was separated and the aqueous layer was extracted with 100 ml. of chloroform. The combined extracts were dried over magnesium sulfate and concentrated to a glass *in vacuo*. Trituration of the glass with hot absolute ethanol and filtration gave 4.70 g. (30%) of white crystals, m.p. 128–135° (changing to glass). The original filtrate was poured into 200 ml. of ice and water and made basic with ammonium hydroxide. Extraction with three 100-ml. portions of chloroform, drying the combined extracts over magnesium sulfate, and concentration of the extract *in vacuo* gave a black glass. The last traces of pyridine were removed by distillation of added benzene. The dark glass was crystallized from hot absolute ethanol to afford 5.0 g. (33%) of 8 as tan crystals, m.p. 128–135° (changes to glass). A 0.500-g. sample was recrystallized once from ethanol to give 0.300 g. of white crystals, changing to a clear glass at 132–138°, liquefying and decomposing at 285–290°, $[\alpha]^{25}D$ +76° (*c* 1.2, pyridine).

Anal. Calcd. for $C_{28}H_{32}N_2O_5S$: C, 66.1; H, 6.34; N, 5.51; S, 6.30. Found: C, 66.0; H, 6.61; N, 5.39; S, 6.03.

β-Yohimbine O-*p*-Toluenesulfonate (7).—To a solution of 10.6 g. (0.030 mole) of β-yohimbine in 50 ml. of cold dry pyridine was added 15.5 g. (0.090 mole) of *p*-toluenesulfonyl chloride. The mixture was allowed to stand at room temperature for 16 hr. Since the mixture had become a solid mass an additional 50 ml. of dry pyridine and 25 ml. of chloroform were added. After standing for an additional 52 hr. the mixture was filtered and the precipitate was washed with chloroform. The precipitate was added to a mixture of 150 ml. of cold water and 100 ml. of chloroform and made basic with ammonium hydroxide. The mixture was stirred, the chloroform layer was removed, and the aqueous layer was extracted with 100 ml. of chloroform. The combined chloroform extracts were dried over magnesium sulfate and concentrated *in vacuo*. Absolute ethanol and benzene were added and the solvent again was removed *in vacuo* to give pale yellow crystals. Trituration of the solid with absolute ethanol and filtration afforded 11.5 g. (75%) of 7 as tan crystals, m.p. 205–208° dec. A 1.0-g. sample was recrystallized from absolute ethanol–chloroform to give 0.740 g. of white needles, m.p. 202–204° dec., $[\alpha]^{25}D$ −1° (*c* 1.5, pyridine).

Anal. Calcd. for $C_{28}H_{32}N_2O_5S$: C, 66.1; H, 6.34; N, 5.51; S, 6.30. Found: C, 66.1; H, 6.28; N, 5.26; S, 6.40.

Yohimban-17-one (3) from β-Yohimbine O-*p*-Toluenesulfonate (7).—A mixture of 0.90 g. (1.77 mmoles) of 7, 0.315 g. (2.2 mmoles) of tripropylamine, and 9 ml. of dry dimethyl sulfoxide was heated under nitrogen at 125–130° in an oil bath for 44 hr. The solvent was removed *in vacuo* and the residue was dissolved in 50 ml. of dichloromethane. The dichloromethane was washed with 15 ml. of 5% sodium carbonate solution and the aqueous layer was extracted once with 20 ml. of dichloromethane. The combined dichloromethane extracts were washed with water, dried over magnesium sulfate, and concentrated *in vacuo*. The residue was warmed on a steam bath with dilute aqueous hydrochloric acid for 30 min. and the solution was made basic with sodium hydroxide. Extraction with dichloromethane, concentration of the extracts, and crystallization of the residue from methanol gave 0.130 g. (25%) of 3, m.p. 295–300° dec., lit.[2a] m.p. 307° dec. Additional ketone could not be obtained from the mother liquors.

Apoyohimbine (9) from Yohimbine O-*p*-Toluenesulfonate (8).—Treatment of 8 with dimethyl sulfoxide and tripropylamine as for 9, followed by chromatography of the product on alumina, gave a 38% yield of 9, m.p. 242–244° dec. (identical with an authentic sample[10] by its infrared spectrum; a mixture melting point showed no depression).

(10) G. Barger and E. Field, *J. Chem. Soc.*, **107**, 1025 (1915).

18-Carboxy-17,18-secoyohimban-17-oic Acid (4).—A mixture of 10.52 g. (0.030 mole) of yohimbinone (2), 3.0 g. of potassium hydroxide, and 75 ml. of absolute ethanol was warmed gently for 2 hr. (not refluxing) and was then refluxed for 2 hr. The solvent was removed *in vacuo* and the residue was dissolved in 50 ml. of water. The mixture was chilled overnight and filtered. The precipitate was washed thoroughly with water and recrystallized from ethanol–water to give 0.13 g. (1.4%) of yohimban-17-one. The filtrate was chilled and brought to pH 7.0 with glacial acetic acid. Chilling and filtering gave 8.4 g. (78%) of **4** as tan crystals, m.p. 195–200° (with previous sintering). Recrystallization of a sample twice from ethanol–water (2:3) with the aid of Darco gave white crystals: these change to a viscous mass at 204–207° and then slowly melt; $[\alpha]^{25}D$ +19° (*c* 1.0, pyridine); ν_{max}^{KBr} 1721 (s) and 1565 (s) cm.$^{-1}$.

Anal. Calcd. for $C_{20}H_{24}N_2O_4$: C, 67.4; H, 6.79; N, 7.86. Found: C, 67.4; H, 6.99; N, 7.46.

Yohimban-17-one (3) from Yohimbinone (2).—A mixture of 2.10 g. of **2** hydrochloride, 100 ml. of 3 *N* hydrochloric acid, and 25 ml. of glacial acetic acid was refluxed for 4 hr. The mixture was cooled and poured into a mixture of ice and 75 ml. of concentrated ammonium hydroxide. Filtration gave a tan solid which was dissolved in ethanol–dichloromethane and the solution was concentrated *in vacuo*. The residue was triturated with methanol to give 0.90 g. (57%) of **3**, m.p. 292–295° dec. A second crop (0.65 g., m.p. 285–288° dec.) was obtained from the filtrate. The solids were combined and recrystallized by dissolving in hot methanol–dichloromethane and boiling off the dichloromethane. There was obtained 1.30 g. (82%) of light tan crystals, m.p. 298–303° dec.

Acknowledgment.—We wish to express our thanks to Mr. L. M. Brancone and staff for elemental analyses, Mr. W. Fulmor and staff for spectral determinations, and Mr. C. Beck for a large-scale preparation.

Correlation of the Proton Magnetic Resonance Chemical Shifts of Substituted Purines with Reactivity Parameters. I. 2,6-Disubstituted Purines

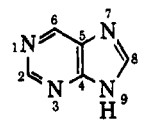
W. C. COBURN, JR., MARTHA C. THORPE, JOHN A. MONTGOMERY, AND KATHLEEN HEWSON

Southern Research Institute, Birmingham, Alabama 35205

Received November 16, 1964

Spin–spin coupling of the 2- and 6-protons of purine has been observed in trifluoroacetic acid solutions ($J_{2,6}$ = 1.05 ± 0.05 c.p.s.) and in aqueous acid ($J_{2,6}$ = 1.05 ± 0.05 c.p.s.). Protonation at N-1 in acid solutions, reducing the asymmetry of the electric field about N-1 and thus allowing spin–spin coupling between H-2 and H-6 to take place without quadrupole relaxation, is offered as an explanation for the observation of splitting in acid but not in neutral solution. Long-range coupling of H-6 and H-8 is also observed in acid, $J \cong 0.3$ c.p.s. Study of the proton magnetic resonance spectra of sixteen 2,6-disubstituted purines in dimethyl sulfoxide solution yielded a linear correlation of the chemical shift of the 8-proton with Brown's electrophilic substituent constant, $\delta_{H\text{-}8} = (8.658 \pm 0.017) + (0.342 \pm 0.016)\Sigma_{2,6}\sigma_p^+$, where $\delta_{H\text{-}8}$ is in parts per million downfield from internal tetramethylsilane. The standard deviation in $\delta_{H\text{-}8}$ is ±0.066 p.p.m. and the correlation coefficient is 0.984. No other substituent parameter tried fit the data as well as σ_p^+.

Recently, several workers have attempted to predict on the basis of theoretical considerations the relative positions of the proton magnetic resonance (p.m.r.) absorption peaks of the three C–H protons of purine (I).[1,2,3a] Experimental determinations of the correct sequence (H-6 at lowest field and H-8 at highest field) in aqueous solutions have been reported by Matsuura and Goto,[4] by Schweizer, Chan, Helmkamp, and Ts'o,[3] and by Bullock and Jardetzky.[5a] Although these theoretical predictions have been successful in rationalizing the relative order of the C–H peaks in the spectrum of the parent purine molecule, especially when compared with the more intuitive predictions of Jardetzky and Jardetzky[5b] and of Reddy, Mandell, and Goldstein,[6] only moderate success may be claimed for the correlation of the chemical shifts of substituted purines with excess charge density.[1]



I

In the course of the routine examination of the p.m.r. spectra of potential anticancer agents, we have obtained the spectra of a number of simply substituted purines. In view of the difficulties of theoretically estimating the effect of substituents in the 2- and 6-positions on the chemical shift of the 8-proton, we have examined several empirical correlations of chemical shifts with reactivity parameters, such as the Hammett σ constants. This report summarizes the results of such correlations for 2,6-disubstituted purines, together with some additional p.m.r. data on unsubstituted purine.

Experimental

Solvents.—Dimethyl sulfoxide-d_6 was obtained from either Merck Sharp and Dohme of Canada Limited or from Stohler Isotope Chemicals, Montreal. Ordinary dimethyl sulfoxide was employed in some cases, where no interference from solvent absorption was expected, and was obtained from Matheson Coleman and Bell. Both of these solvents were dried over a Linde 4A Molecular Sieve before use. Trifluoroacetic acid was an Eastman Kodak reagent and was used without prior treatment. Deuterium oxide was obtained from General Dynamics Corporation.

Purines.—Purine-d_0 was bought from Francis Earle Laboratories, Inc., and was found to be chromatographically homogeneous.

The preparations of most of the substituted purines have been previously reported. One exception is 2-chloro-6-methoxypurine. A solution of 2,6-dichloropurine (1 g., 5 mmoles) in 1 *N* sodium

(1) A. Veillard, *J. chim. phys.*, **59**, 1056 (1962).
(2) P. G. Lykos and R. L. Miller, *Tetrahedron Letters*, **No. 25**, 1743 (1963).
(3) (a) M. P. Schweizer, S. I. Chan, G. K. Helmcamp, and P. O. P. Ts'o, *J. Am. Chem. Soc.*, **86**, 696 (1964); (b) S. I. Chan, M. P. Schweizer, P. O. P. Ts'o, and G. K. Helmcamp, *ibid.*, **86**, 4182 (1964).
(4) S. Matsuura and T. Goto, *Tetrahedron Letters*, **No. 22**, 1499 (1963).
(5) (a) F. J. Bullock and O. Jardetzky, *J. Org. Chem.*, **29**, 1988 (1964); (b) C. D. Jardetzky and O. Jardetzky, *J. Am. Chem. Soc.*, **82**, 222 (1960).
(6) G. S. Reddy, L. Mandell, and J. H. Goldstein, *J. Chem. Soc.*, 1414 (1963).