Anal. Calcd. for $C_{25}H_{23}N_5O_5S_2$: N, 8.20; S, 9.30. Found: N, 8.15; S, 9.69.

Upon methylation with methyl iodide, however, a 5-methoxy-N-methyl-N-toluene *p*-sulfonyltryptamine whose melting point coincided with the literature value was obtained, m.p. 117–120° (lit.[21] m.p. 118–119°). It was then possible to convert this tosylate with liquid ammonia in good yield to a very pure, hitherto unreported, 5-methoxy-N-methyltryptamine base by modifying the literature procedure somewhat. Thus, instead of ether extraction of the water solution of the ammonia detosylation residue, the solid that precipitated was filtered, washed, and dried. In this manner 347 mg. (9.3×10^{-4} mole) of 5-methoxy-N-methyl-N-toluene-*p*-sulfonyltryptamine yielded 127 mg. (67%) of 5-methoxy-N-methyltryptamine, m.p. 99–102°.

Anal. Calcd. for $C_{12}H_{16}N_2O$: C, 70.55; H, 7.90; N, 13.72. Found: C, 70.41; H, 7.79; N, 13.50.

A picrate was prepared in the usual manner; 136 mg., m.p. 224–226° dec., was obtained from 75 mg. of the free base.

Anal. Calcd. for $C_{18}H_{18}N_5O_8$: C, 50.00; H, 4.19; N, 16.20. Found: C, 50.61; H, 4.51; N, 15.77.

5-Methoxy-2-oxo-2,3-dihydrotryptamine.—5-Methoxy-3-oxindolylacetonitrile was prepared starting from 5-methoxyisatin and cyanoacetic acid.[22] The nitrile (9 g., 0.045 mole) was hydrogenated in 100.0 ml. of ethanol and 9.0 ml. of concentrated hydrochloric acid over 0.5 g. of platinum oxide catalyst at 2.8 kg./cm.^{2} for 2.5 hr. The reaction mixture was filtered through Celite and all of the solvents were removed under vacuum. The product was crystallized from ethanol–chloroform. In several crops, a total of 5.8 g. (69% yield) of product was isolated. The crops varied in melting points from 270 to 275° with the first crop having the best purity, m.p. 275° dec.

Anal. Calcd. for $C_{11}H_{15}ClN_2O_2$: C, 54.39; H, 6.23; Cl, 14.61; N, 11.54. Found: C, 54.41; H, 6.22; Cl, 14.75; N, 11.47.

Serotonin Antagonism.—The myotropic response to a standard dose of 0.4 μg. of serotonin was determined using estrus rat uterus, in a muscle bath. The potency of compounds in the series was determined by the amount required to antagonize the action of the standard. If less than 5 μg. of compound was required for antagonism it was rated as 4+, 5–20 μg. as 3+, 20–50 as 2+, 50–100 μg. as +, more than 100 μg. as no activity. Results are given in Table I.

Effect on Behavior.—The effect of compounds on behavior was determined in the following manner. Rats were conditioned on a variable interval (V.I.) positive reinforcement schedule, *i.e.*, bar pressing in a Skinner box at a steady medium rate which was rewarded automatically with food pellets. Faster or slower rates therefore represented less reward for effort and would indicate that behavior was not optimal. Animals were deprived of food and spent 50 min. each day in the test chamber. The mean rate of response during each quarter of the test period on 5 consecutive days was determined. On the experimental day the compound was administered intraperitoneally, and the increased (+) or decreased (−) response rates were computed as a percentage of the normal. Many rats were used to determine the effect of each compound, and several dose levels were employed. Specific examples to illustrate the action of each compound are quoted in Table I.

Acknowledgment.—The authors wish to thank Martin Kampe for his exceptionally fine technical assistance.

Acyltryptamines. III. 5-Acetyltryptophan and Related Compounds

MAXIMILIAN VON STRANDTMANN, CHESTER PUCHALSKI, AND JOHN SHAVEL, JR.

Warner-Lambert Research Institute, Morris Plains, New Jersey

Received August 23, 1963

A number of 5-acetylindole derivatives, such as 5-acetyltryptophan, 5-acetylheteroauxin, 5-acetylskatole, 5-acetylgramine, 5-acetyl-N,N-dimethyltryptamine, 6-acetyl-1,2,3,4-tetrahydronorharman, various 1-substituted 6-acetyl-1,2,3,4-tetrahydro-β-carbolines, and 10-acetyl-17,18-dimethoxy-15,16,17,18,19,20-hexadehydroyohimbane were synthesized. Most of these compounds produced hypotensive effects in dogs.

The introduction of the acetyl group into position 5 of the tryptamine molecule results in a significant change in its pharmacological properties.[1] This finding suggested the preparation of 5-acetyl analogs of other indole-containing substances of physiological significance. The present investigation concerns itself with the synthesis of derivatives of gramine, skatole, N,N-dimethyltryptamine, tryptophan, heteroauxin, β-carboline, and yohimbane, which are substituted by acetyl groups in the position *para* to the indole nitrogen.

It has been shown in the course of this work that the acetyl group at C-5 of the indole nucleus can survive the conditions of catalytic –C–N– hydrogenolysis as well as a variety of acid- and base-catalyzed condensation reactions. A survey of the literature suggested that all of the desired compounds could be synthesized starting from 5-acetylgramine (I) and 5-acetyltryptamine (II). Our first task, therefore, centered upon the preparation of 5-acetylgramine. The problem was approached by two routes. One involved the formation of the indole nucleus in the course of the synthesis; the other utilized preformed 5-acetylindole as the starting material.

The first route was an adaptation of Hegedüs'[2] tryptophan synthesis which had the advantage of also being applicable to the synthesis of 5-acetyl-N,N-dimethyltryptamine (III). The synthetic scheme involved a Japp–Klingemann coupling of diazotized *p*-aminoacetophenone with ethyl α-(2-dimethylaminoethyl)acetoacetate (IV) and ethyl α-(3-dimethylaminopropyl)acetoacetate (V) to give the *p*-acetylphenylhydrazones of ethyl α-keto-γ-dimethylaminobutyrate (VI) and of ethyl α-keto-δ-dimethylaminovalerate (VII). Cyclization of the hydrazones with polyphosphoric acid gave 5-acetyl-2-carbethoxygramine (VIII) and 5-acetyl-2-carbethoxy-N,N-dimethyltryptamine (IX), respectively. However, decarbethoxylation of ester VIII as well as decarboxylation of 5-acetyl-2-carboxygramine (X), obtained by hydrolysis of VIII, proved to be very difficult. Heating with resorcinol,[3] sulfuric acid, or hydrobromic acid resulted solely in extensive decomposition, whereas prolonged refluxing in hydrochloric acid–acetic acid gave 5-acetylgramine (I) in a maximum yield of 2.5%.[4] The slow rate of decarboxylation of this compound is in

(1) (a) J. Shavel, Jr., M. von Strandtmann, and M. P. Cohen, *J. Am. Chem. Soc.*, **84**, 881 (1962); (b) M. von Strandtmann, M. P. Cohen, and J. Shavel, Jr., 141st National Meeting of the American Chemical Society, Washington, D.C., March, 1962.

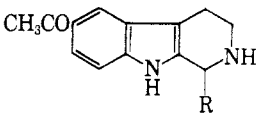
(2) B. Hegedüs, *Helv. Chim. Acta*, **29**, 1499 (1946).

(3) H. Plieninger, *Ber.*, **83**, 268 (1950).

(4) Uncorrected for recovered acid X.

TABLE I

6-ACETYL-1,2,3,4-TETRAHYDRO-β-CARBOLINES



Compd.	R	Method	% yield	M.p., °C.	Formula	% calcd. C	% calcd. H	% calcd. N	% found C	% found H	% found N
XXIV	CH_3	C	41	194–196	$C_{14}H_{16}N_2O$	73.65	7.06	12.27	73.42	7.15	11.99
				Dec. above 250	$C_{14}H_{16}N_2O \cdot HCl$	63.51	6.47	10.58	63.69	6.27	10.57
XXV	C_6H_5	B	37	196–202	$C_{19}H_{18}N_2O$	78.59	6.25	9.65	78.36	6.43	9.40
				85–92	$C_{19}H_{18}N_2O \cdot C_2H_5OH$	74.97	7.19	8.35	75.05	7.06	8.51
XXVI	$C_6H_5CH_2$	A	30	150–153	$C_{20}H_{20}N_2O$	78.92	6.62	9.20	78.68	6.82	9.24
				287–293 dec.	$C_{20}H_{20}N_2O \cdot HCl$	70.47	6.21	8.22	70.58	6.12	8.00
XXVII	CH_3O–C$_6$H$_4$–CH_2	A	31	287–290	$C_{21}H_{22}N_2O_2 \cdot HCl$	68.01	6.25	7.55	67.99	6.45	7.27
XXVIII	$(CH_3O)_2$–C$_6$H$_3$–CH_2	A	31	275–277	$C_{22}H_{24}N_2O_3 \cdot HCl$	65.91	6.28	6.99	65.83	6.50	6.81
XXIX	$C_6H_5CH_2CH_2$	A	54	292–294	$C_{21}H_{22}N_2O \cdot HCl$	71.07	6.53	7.89	71.05	6.78	7.82

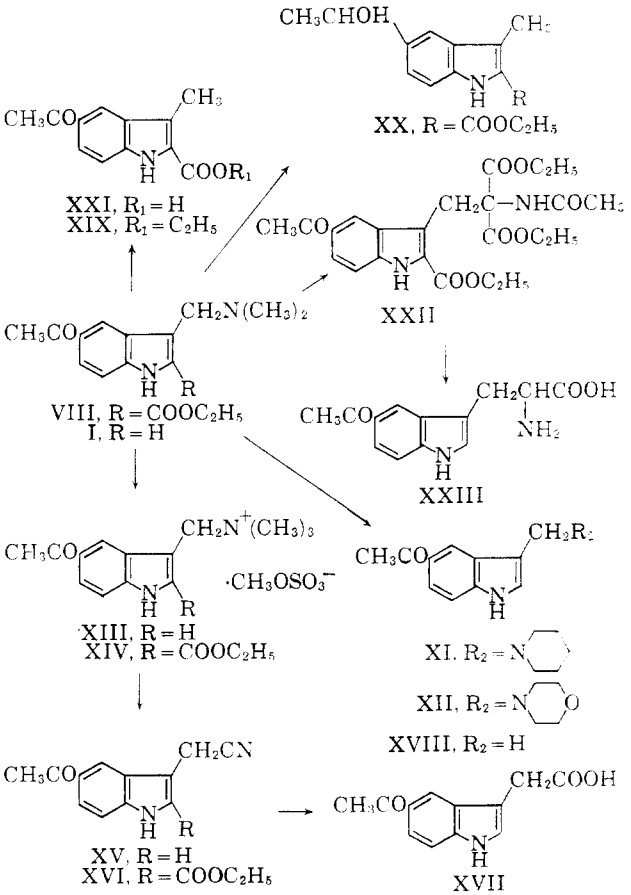
agreement with Abramovitch's[5] assumption that protonation of the indole nitrogen is the rate-determining step of this reaction. Evidently, this step is retarded by the positive charge created by the protonation of the dimethylaminomethyl moiety. Support for this explanation is furnished by the behavior of 5-acetyl-2-carbethoxy-N,N-dimethyltryptamine (IX), whose basic moiety is further removed from the vicinity of the indole nitrogen. This compound is easily decarbethoxylated by refluxing hydrochloric acid to 5-acetyl-N,N-dimethyltryptamine (III).

The low yields of 5-acetylgramine obtained by the preceding reaction sequence necessitated development of an alternate approach to this key intermediate. A simple one-step process modeled after Kuhn's synthesis of gramine,[6] the Mannich condensation of 5-acetylindole[7] with formaldehyde and dimethylamine, was found to give I in excellent yields.

Thus, having secured an adequate source of 5-acetylgramine and 5-acetyl-2-carbethoxygramine, we began to investigate the usefulness of these intermediates in reactions characteristic of gramine, such as transamination,[8] hydrogenolysis,[9] and C-alkylation.[8,10]

Transamination of 5-acetylgramine with refluxing piperidine and morpholine resulted in the formation of 5-acetyl-3-piperidinomethylindole (XI) and 5-acetyl-3-morpholinomethylindole (XII), respectively.

Quaternization with methyl sulfate gave the methosulfates of 5-acetylgramine (XIII) and 5-acetyl-2-carbethoxygramine (XIV), of which only the first was isolated and characterized. Both quaternaries were treated with sodium cyanide in aqueous medium to give 5-acetyl-3-(cyanomethyl)indole (XV) and 5-acetyl-2-carbethoxy-3-(cyanomethyl)indole (XVI). Acid hydrolysis of 5-acetyl-3-(cyanomethyl)indole gave 5-acetylindole-3-acetic acid (XVII).



Hydrogenation of 5-acetylgramine and 5-acetyl-2-carbethoxygramine over palladium-on-charcoal gave 5-acetylskatole (XVIII) and 5-acetyl-2-carbethoxyskatole (XIX). If this reaction was not interrupted after 1 mole of hydrogen was taken up, reduction of the carbonyl group took place as was demonstrated by the conversion of 5-acetyl-2-carboethoxygramine to D,L-5-(α-hydroxyethyl)-2-carbethoxyskatole (XX).

(5) R. A. Abramovitch, *J. Chem. Soc.*, 4593 (1956).

(6) H. Kuhn and O. Stein, *Ber.*, **70**, 567 (1937).

(7) Prepared by dehydrogenation of 5-acetylindoline (Aldrich Chemical Co.) according to A. P. Terentiev, M. N. Preobrazhenskaia, and G. M. Sorokina, *J. Gen. Chem. USSR*, **29**, 2875 (1959); *Chem. Abstr.*, **54**, 12098 (1960).

(8) E. E. Howe, A. J. Zambito, H. R. Snyder, and M. Tishler, *J. Am. Chem. Soc.*, **67**, 38 (1945).

(9) (a) A. P. Terentiev, N. A. Dzbanovskii, and N. A. Favorskaya, *J. Gen. Chem. USSR*, **23**, 2035 (1953); (b) B. Marchand, *Chem. Ber.*, **95**, 577 (1962).

(10) (a) C. Schöpf and J. Thessing, *Angew. Chem.*, **63**, 377 (1951); (b) J. Thessing and F. Schulde, *Chem. Ber.*, **85**, 324 (1952).

TABLE II

Compd.	ALD_{50}[a] mg./kg. p.o.	Dose, mg./kg. i.v.	Hypotensive effect, mm.	Duration of the effect, min.	Response to reference agents and remarks
I	90	5	20–40	<10	Potentiates response to DMPP.[b] Blocks response to epinephrine, acetylcholine, renin histamine.
		10	>40	>30	
III	240	0.1	20–40	>30	Cardiotoxic. Respiratory failure at 1 mg./kg. Blocks response to histamine. Potentiates response to DMPP.
		0.5	>40	>30	
		1			
VIII	300	1	<20	<10	Potentiates response to DMPP.
		10	>40	10–30	
IX	750	2.5	>40	<10	Precipitous fall in blood pressure, accompanied by bradycardia. Cardiotoxic.
		5	>40	10–30	
XI	200	0.1	0		Respiratory stimulation in the direction of an increase of tidal volume. Increase in pulse pressure.
		10	<20	<10	
XII	400	0.1	0		Vasodilation
		1	<20	<10	
		10	<20	>30	
XXII	>1000				Not tested
XXIII	>1000	10			Inactive
XXIV	>1000	0.1	<20	10–30	Blocks response to epinephrine, norepinephrine, DMPP.
		1	<20	>30	
XXV	>1000	0.1	0		Blocks response to epinephrine. Moderate blood pressure fall of long duration.
		1	0		
		10	20–40	>30	
XXVI	>1000	0.1	0		Potentiates response to epinephrine, norepinephrine, DMPP. Produces respiratory depression.
		1	<20	<10	
		10	<20	>30	
XXVII	600	0.1	0		
		1	20–40	<10	
XXVIII	150	0.1	0		Blocks response to epinephrine, norepinephrine, acetylcholine, histamine, DMPP, carotid occlusion, renin.
		1	<20	<10	
		10	>40	10–30	
XXIX	>1000	2.5	<20	<10	10 mg./kg. lethal. Blocks response to epinephrine, norepinephrine, acetylcholine, carotid occlusion. Potentiates response to histamine.
		10			
XXX	>1000				Not tested.

[a] Approximate LD_{50}. [b] 1,1-Dimethyl-4-phenylpiperazinium iodide.

Of interest here is the shift of the ester carbonyl frequencies in the infrared, caused by removal of the basic moiety. As a result, the absorption bands of the carbethoxy groups of skatole-type compounds, such as XIX and XX, are found in the 1660–1670-cm.$^{-1}$ region which is also characteristic of the ketonic carbonyl at C-5. That reduction of the ketone moiety of VIII to the alcohol group of XX had indeed occurred is evident from a hypsochromic shift of the main absorption band in the ultraviolet from the 260–270-mμ region, characteristic of 5-acetyl-2-carboxy (or carbethoxy) indoles, to the 230-mμ region, characteristic of an α-hydroxyethyl group at C-5.

In accord with the above considerations concerning the mechanism of decarboxylation, 5-acetyl-2-carboxyskatole (XXI), obtained by hydrolysis of 5-acetyl-2-carbethoxyskatole, was found to decarboxylate easily to 5-acetylskatole.

The alkylation of diethyl 2-acetamidomalonate by 5-acetyl-2-carbethoxygramine, in refluxing toluene in the presence of powdered sodium hydroxide, gave 5N,-diacetyl-2,α,α-tricarbethoxytryptamine (XXII) in quantitative yield. Hydrolysis and decarboxylation of this triester in refluxing hydrochloric acid–acetic acid mixture gave 5-acetyltryptophan hydrochloride (XXIII), which displayed a typical α-amino acid carbonyl absorption band in the infrared at 1743 cm.$^{-1}$.

The acyl derivatives of β-carboline and hexadehydroyohimbane were prepared from 5-acetyltryptamine using methods adapted from Tatsui's[11a] and Akabori's[11b] synthesis of tetrahydronorharmanes and from Hahn's[12] synthesis of hexadehydroyohimbanes.

The acid-catalyzed condensation of 5-acetyltryptamine with acetaldehyde gave 6-acetyl-1,2,3,4-tetrahydronorharmane (XXIV). Extension of this reaction with benzaldehyde, phenylacetaldehyde, hydrocinnamaldehyde, *p*-methoxyphenylpyruvic acid, and 3,4-dimethoxyphenylpyruvic acid yielded the corresponding 1-substituted 6-acetyl-1,2,3,4-tetrahydro-β-carbolines XXV–XXIX (Table I). The condensation of 6-acetyl-1-(3,4-dimethoxybenzyl)-1,2,3,4-tetrahydro-β-carboline with formaldehyde gave 10-acetyl-17,18-dimethoxy-15,16,17,18,19,20-hexadehydroyohimbane (XXX). The possibility of the condensation having taken place *ortho* to the methoxyl group rather than *para* is unlikely, since it has been shown that 6,7-methylenedioxy-1-(3,4-dimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline is cyclized at the position *para* to the methoxyl.[13]

Summary of Pharmacological Data.—The cardiovascular effects were evaluated in anesthetized dogs by the method described in the preceding paper of this series.[14] The results are summarized in Table II. At high dose levels the β-carboline-type compounds XXIV–

(11) (a) G. Tatsui, *J. Pharm. Soc. Japan*, **48**, 92 (1928); (b) S. Akabori and K. Saito, *Ber.*, **63**, 2245 (1930).

(12) G. Hahn and H. Werner, *Ann.*, **520**, 123 (1935).

(13) R. D. Haworth, W. H. Perkin, Jr., and J. Rankin, *J. Chem. Soc.*, 1686 (1924).

(14) M. von Strandtmann, M. P. Cohen, and J. Shavel, Jr., *J. Med. Chem.*, **6**, 719 (1963).

XXIX elicited a moderate depressor response of long duration. The low oral toxicity characteristic of this class, was significantly increased by the introduction of methoxyl groups into the benzyl substituent. This elevated toxicity, shown by XXVII and XXVIII, was accompanied by a decrease of the duration of the hypotensive effect. Compounds of the 3-(dimethylaminoalkyl)indole type (I, III, VIII, IX, XI, and XII) were generally more toxic. The toxicity of this class was decreased by the presence of the carbethoxy group at C-2 (VIII, IX). However this decrease was paralleled by a shortening of the duration of the hypotensive response. N,N-dimethyltryptamine-type compounds, III and IX, the most active of the series, produced a precipitous blood pressure fall and arrhythmia, which might be indicative of cardiotoxicity. The surprising lack of activity shown by 5-acetyltryptophan (XXIII) suggests that this compound is not metabolized to 5-acetyltryptamine.

Experimental[15]

Ethyl α-Keto-γ-dimethylaminobutyrate *p*-Acetylphenylhydrazone (VI).—A solution of 40 g. of *p*-aminoacetophenone in 250 ml. of water and 143 ml. of concd. HCl was diazotized at 0–5° with 21 g. of sodium nitrite in 200 ml. of water. To the resulting solution of *p*-acetylphenyldiazonium chloride was added 60.3 g. of ethyl α-(2-dimethylaminoethyl)acetoacetate followed by 63 g. of sodium acetate. The pH was raised to 6–7 and maintained in this range by addition of 3 *N* sodium hydroxide. The mixture was stirred in the cold for 2 hr., made basic, and extracted with three 400-ml. portions of chloroform. Combined extracts were dried over sodium sulfate and concentrated *in vacuo*. The residue crystallized from benzene–petroleum ether after purification with charcoal, yield 65 g. (68%). An analytical sample was obtained by two crystallizations from petroleum ether, m.p. 84–85°.

Anal. Calcd. for $C_{16}H_{23}N_3O_3$: C, 62.93; H, 7.59; N, 13.76. Found: C, 63.19; H, 7.82; N, 14.00; λ_{max}, mμ (ε) 236 (9900) 351 (41,100); ν_{max} 1685 (s), 1668 (m), 1630 (m), 1603 (s), 1575 (m), 1550 (m), and 1513 (m) cm.$^{-1}$.

5-Acetyl-2-carbethoxygramine Hydrochloride (VIII).—A mixture of 43 g. of ethyl α-keto-γ-dimethylaminobutyrate *p*-acetylphenylhydrazone and 430 g. of polyphosphoric acid was heated slowly with stirring. At 60–65° an exothermic reaction took place accompanied by foaming which resulted in a large increase in the volume of the reaction mixture. The temperature was gradually raised to 100–110° and maintained for 2 hr. After being cooled to 70°, the viscous solution was poured into 700 ml. of ice-water. The aqueous mixture was stirred to complete solution, made basic at low temperature, and extracted with three 400-ml. portions of chloroform. The combined chloroform extracts were dried over sodium sulfate and evaporated *in vacuo*. A solution of the residue in 150 ml. of ethanol was treated with ethanolic HCl and allowed to stand overnight. The precipitated salt was filtered off and recrystallized from 95% ethanol, yield 37%, m.p. 211–214°.

Anal. Calcd. for $C_{16}H_{20}N_2O_3 \cdot HCl$: C, 59.16; H, 6.52; N, 8.63. Found: C, 59.21; H, 6.82; N, 8.89; λ_{max}, mμ (ε) 264 (50,500), 312.5 (10,500), 321.7 (9400); ν_{max} 720, 783, 835, 1018, 1582, 1618, 2880 (m), 1250, 1690 (s), 1667, and 3280 (ms) cm.$^{-1}$.

5-Acetyl-2-carboxygramine (X).—A solution of 0.5 g. of 5-acetyl-2-carbethoxygramine in 10 ml. of 18% hydrochloric acid was refluxed for 18 hr. After chilling, the precipitate was collected on a filter, decolorized with charcoal, and crystallized twice from 65% ethanol, m.p. 219–222°.

Anal. Calcd. for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20; N, 10.76. Found: C, 64.64; H, 6.48; N, 10.64; λ_{max}, mμ (ε) 260.7 (51,300); 303 (8800); ν_{max} 3150 (m), 1657 (s), 1605 (s), 1573 (m), and 1548 (w) cm.$^{-1}$.

5-Acetylgramine (I) from 5-Acetyl-2-carbethoxygramine.—A solution of 30 g. of 5-acetyl-2-carbethoxygramine hydrochloride in 300 ml. of acetic acid and 900 ml. of 20% hydrochloric acid was refluxed for 125 hr. After cooling, the precipitated 5-acetyl-2-carboxygramine (20 g.) was filtered. The filtrate was made basic in the cold with 40% potassium hydroxide solution and extracted with chloroform. The combined extracts were dried over sodium sulfate and concentrated *in vacuo*. The oily residue, which crystallized on standing, was recrystallized from benzene, m.p. 142–144°, yield 0.5 g.

Anal. Calcd. for $C_{13}H_{16}N_2O$: C, 72.19; H, 7.46; N, 12.92. Found: C, 71.98; H, 7.61; N, 12.94; λ_{max}, mμ (ε) 251 (33,800), 296 (8400); ν_{max} 3150 (m), 1675 (s), 1625 (m), 1586 (m), 1552 (m) cm.$^{-1}$.

***p*-Acetylphenylhydrazone of Ethyl α-Keto-δ-dimethylaminovalerate (VII).**—Compound VII was prepared analogous to VI using 70 g. of ethyl α-(3-dimethylaminopropyl)acetoacetate. The pH of this reaction mixture was maintained at 5.5–6, yield 98 g. (95%), m.p. 87–94°. An analytical sample was prepared by treatment of an ethereal solution of the hydrazone with ethereal hydrogen chloride and two crystallizations of the resulting salt from acetone, m.p. 166–168°.

Anal. Calcd. for $C_{17}H_{25}N_3O_3 \cdot HCl$: C, 57.37; H, 7.36; N, 11.81. Found: C, 57.38; H, 7.57; N, 11.72; λ_{max}, mμ (ε) 236 (9500), 348 (40,000); ν_{max} 855 (m), 1150 (s), 1225 (ms), 1248, (s), 1592 (vs), 1668 (m), and 1697 (ms) cm.$^{-1}$.

5-Acetyl-2-carbethoxy-N,N-dimethyltryptamine (IX).—Compound IX was prepared by the polyphosphoric acid cyclization of the *p*-acetylphenylhydrazone of ethyl α-keto-δ-dimethylaminovalerate analogous to the preparation of VIII. The viscous reaction product was dissolved in ethyl acetate, and the solution was filtered and treated with ethereal hydrogen chloride. The precipitated hydrochloride was filtered off, washed with dry ether, and extracted with 1 l. of acetonitrile. Upon concentration and chilling of the extract 2.6 g. (15%) of product was obtained, m.p. 244–245°.

Anal. Calcd. for $C_{17}H_{22}N_2O_3 \cdot HCl$: C, 60.26; H, 6.84; N, 8.27. Found: C, 60.09; H, 6.75; N, 8.06; λ_{max}, mμ (ε) 268.3 (52,500), 313.7 (8500); ν_{max} 785 (m), 830 (ms), 1545 (mw), 1577 (ms), 1615 (m), 1650, 1662 sh (s), 1700 (vs), 2680 (m), and 3100 (m) cm.$^{-1}$.

5-Acetyl-N,N-dimethyltryptamine (III).—A solution of 11.2 g. of 5-acetyl-2-carbethoxy-N,N-dimethyltryptamine hydrochloride in 190 ml. of 20% hydrochloric acid was refluxed for 4.5 hr., chilled, filtered, made basic in the cold with 40% potassium hydroxide solution, and extracted with four 125-ml. portions of chloroform. The combined extracts were dried over sodium sulfate and evaporated *in vacuo*. A solution of the residue in ethyl acetate was filtered and treated with ethereal hydrogen chloride. The precipitated salt was filtered off and recrystallized from acetonitrile, yield 1.8 g. (21%), m.p. 227–228°.

Anal. Calcd. for $C_{14}H_{18}N_2O \cdot HCl$: C, 63.03; H, 7.18; N, 10.50. Found: C, 63.14; H, 7.24; N, 10.72; λ_{max}, mμ (ε) 253 (32,900), 296.5 (7650); ν_{max} 820 (m), 968 (m), 1218 (m), 1248 (m) 1295 (m), 1588 (m), 1625 (mw), 1662 (s), 2750 (ms), and 3300 (ms) cm.$^{-1}$.

5-Acetylgramine (I) from 5-Acetylindole.—A mixture of 15 g. of 5-acetylindole, 7.56 g. of 37% aqueous formaldehyde, 17 g. of 25% aqueous dimethylamine, 25 ml. of acetic acid, and 250 ml. of methanol was refluxed for 3 hr., concentrated *in vacuo* to 20% of its volume, treated with 100 ml. of water, washed with chloroform, chilled, and made basic with 20% sodium hydroxide. The crystalline precipitate was collected on a filter and washed with cold water, yield 17.3 g. (79%). An analytical sample was obtained by two crystallizations from benzene, m.p. 142–145°.

Anal. Calcd. for $C_{13}H_{16}N_2O$: C, 72.19; H, 7.46; N, 12.95. Found: C, 72.16; H, 7.63; N, 12.84; λ_{max}, mμ (ε) 251 (33,400), 296 (8200); ν_{max} 3100 (m), 1673 (s), 1624 (m), and 1585 (m) cm.$^{-1}$.

5-Acetyl-3-piperidinomethylindole (XI).—A solution of 5 g. of 5-acetylgramine in 125 ml. of piperidine was refluxed for 2.5 hr. and concentrated *in vacuo*. The oily residue crystallized upon trituration with petroleum ether, yield 5.2 g. (88%). An analytical sample was prepared by three crystallizations from benzene, m.p. 145–148°.

Anal. Calcd. for $C_{18}H_{26}N_2O$: C, 74.96; H, 7.86; N, 10.93. Found: C, 75.03; H, 8.04; N, 10.80; λ_{max}, mμ (ε) 251 (34,200), 296 (8300); ν_{max} 3080 (w), 1658 (s), 1618 (m), and 1580 (m) cm.$^{-1}$.

5-Acetyl-3-morpholinomethylindole Monohydrate (XII).—A solution of 7 g. of 5-acetylgramine in 200 ml. of morpholine was refluxed for 2.5 hr. and concentrated *in vacuo*. The oily residue

(15) Melting points were determined on a Meltemp melting point apparatus with an aluminum block. Infrared spectra were recorded on a Baird spectrograph, Model No. 455 as Nujol mulls. Ultraviolet spectra were determined on a Beckman DK-1 spectrophotometer in 95% ethanol.

crystallized upon trituration with a small amount of water. The product was purified by recrystallization from water, yield 5 g. (56%), m.p. 49–60°.

Anal. Calcd. for $C_{15}H_{16}N_2O_2 \cdot H_2O$: C, 65.19; H, 7.30; N, 10.14. Found: C, 65.10; H, 7.20; N, 10.11; λ_{max}, mμ (ϵ) 251 (35,200), 296 (8700); ν_{max} 3550 (m), 3150 (m) 1655 (s), 1612 (m), 1242 (s), and 1110 (s) cm.$^{-1}$.

5-Acetylgramine Methosulfate (XIII).—A stirred solution of 2.5 g. of 5-acetylgramine and 1 ml. of acetic acid in 50 ml. of dry tetrahydrofuran was treated at 10° with a solution of 6.3 g. of dimethyl sulfate and 1 ml. of acetic acid in 25 ml. of dry tetrahydrofuran, over a period of 90 min. with protection from moisture. The reaction mixture was then stirred for 2 additional hr. The precipitate was filtered and washed with cold tetrahydrofuran, then with ether, yield 3.6 g. (95%). The analytical sample was prepared by two crystallizations from ethanol, m.p. 170–173°.

Anal. Calcd. for $C_{15}H_{22}N_2O_5S$: C, 52.61; H, 6.48; N, 8.18. Found: C, 52.68; H, 6.51; N, 7.92; λ_{max}, mμ (ϵ) 243 (39,400), 286 (10,300); ν_{max} 3200 (m), 1680 (s), 1620 (m), and 1210 (s) cm.$^{-1}$.

5-Acetyl-2-(cyanomethyl)indole (XV).—A solution of 2.9 g. of 5-acetylgramine methosulfate in 30 ml. of water was combined with a solution of 1.5 g. of sodium cyanide in 20 ml. of water. The reaction mixture was heated on steam for 30 min., chilled, and extracted with chloroform. The extracts were dried over sodium sulfate and evaporated *in vacuo* to yield 1.5 g. (90%) of crystalline residue. An analytical sample was prepared by recrystallization from 95% ethanol, m.p. 125–127°.

Anal. Calcd. for $C_{12}H_{10}N_2O$: C, 72.71; H, 5.08; N, 14.13. Found: C, 72.47; H, 5.19; N, 14.22; λ_{max}, mμ (ϵ) 248 (37,000), 285 (9700), 294 sh (8900); ν_{max} 3330 (m) 2300 (vw), 1650 (s), 1615 (m), and 1573 (m) cm.$^{-1}$.

5-Acetyl-2-carbethoxy-3-cyanomethylindole (XVI).—The uncharacterized methosulfate of VIII was prepared in analogy to XIII. The crude methosulfate, obtained from 7 g. of VIII, was dissolved in 90 ml. of water and combined with a solution of 3.4 g. of sodium cyanide in 40 ml. of water. The reaction mixture was heated on steam for 30 min., the precipitated product was filtered and washed with water, yield 3.56 g. (57%). An analytical sample was obtained by two crystallizations from ethanol, m.p. 215–219°.

Anal. Calcd. for $C_{15}H_{14}N_2O_3$: C, 66.65; H, 5.22; N, 10.36. Found: C, 66.51; H, 5.46; N, 10.43; λ_{max}, mμ (ϵ) 266 (59,000), 310 (10,300); ν_{max} 3350 (s), 2300 (w), 1694 (s), 1678 (s), 1667, sh 1610 (m), 1582 (m), 1255 (s), and 1222 (ms) cm.$^{-1}$.

5-Acetylindole-3-acetic Acid (XVII).—A solution of 5 g. of 5-acetyl-3-cyanomethylindole in 200 ml. of 20% hydrochloric acid was refluxed for 30 min. and filtered hot. Upon chilling of the filtrate a crystalline product precipitated which was collected on filter and recrystallized from acetonitrile, yield 2.17 g. (40%). An analytical sample was obtained by two crystallizations from 50% ethanol, m.p. 193–197° dec.

Anal. Calcd. for $C_{12}H_{11}NO_3$: C, 66.35; H, 5.11; N, 6.45. Found: C, 66.36; H, 5.34; N, 6.51; λ_{max}, mμ (ϵ) 253 (33,700), 297 (8100); ν_{max} 3360 (m), 1730 (s), 1635 (s), 1618 (m), and 1580 (m) cm.$^{-1}$.

5-Acetylskatole (XVIII).—A solution of 1 g. of 5-acetylgramine in 50 ml. of ethanol was hydrogenated at room temperature and atmospheric pressure in the presence of 70 mg. of palladium-on-carbon. After the uptake of one molar equivalent of hydrogen was completed, the catalyst was removed by filtration and the filtrate was evaporated *in vacuo*. A solution of the distillation residue in chloroform was washed twice with 5% hydrochloric acid, dried over sodium sulfate, and evaporated. The crystalline residue was triturated with petroleum ether and collected on a filter, yield 0.55 g. (68%). An analytical sample was prepared by two crystallizations from benzene, m.p. 129–131°.

Anal. Calcd. for $C_{11}H_{11}NO$: C, 76.27; H, 6.40; N, 8.09. Found: C, 76.19; H, 6.36; N, 8.06; λ_{max}, mμ (ϵ) 257 (33,800), plateau 294–302 (7560); ν_{max} 3250 (s), 1650 (s), 1617 (m), 1576 (m), 1308 (m), 1250 (m), 1238 (m), 882 (m), and 805 (m) cm.$^{-1}$.

5-Acetyl-2-carbethoxyskatole (XIX) was prepared from 5-acetyl-2-carbethoxygramine by a procedure analogous to the reduction of 5-acetylgramine, yield 29%, m.p. 174–177°.

Anal. Calcd. for $C_{14}H_{15}NO_3$: C, 68.55; H, 6.16; N, 5.71. Found: C, 68.43; H, 6.10; N, 5.46; λ_{max}, mμ (ϵ) 270 (61,400), 310 (9400), ν_{max} 3300 (m), 1665 (s), 1610 (w), and 1572 (m) cm.$^{-1}$.

D,L-5-(α-Hydroxyethyl)-2-carbethoxyskatole (XX) was prepared from 5-acetyl-2-carbethoxygramine by a method analogous to the reduction of 5-acetylgramine. The reaction was allowed to proceed until the uptake of two molar equivalents of hydrogen was completed, yield 60%, m.p. 142–144°.

Anal. Calcd. for $C_{14}H_{17}NO_3$: C, 67.99; H, 6.93; N, 5.66. Found: C, 67.93; H, 7.23; N, 5.54; λ_{max}, mμ (ϵ) 232 (26,250), 297 (20,650); ν_{max} 3450 (m), 3280 (m), and 1667 (s) cm.$^{-1}$.

5-Acetyl-2-carboxyskatole (XXI).—A suspension of 0.6 g. of 5-acetyl-2-carbethoxyskatole in a mixture of 15 ml. of ethanol and 10 ml. of 20% sodium hydroxide was refluxed for 1 hr. The solution was evaporated *in vacuo* and the residue taken up in water. The aqueous solution was washed with chloroform and made acidic with hydrochloric acid. The precipitate was collected on filter and recrystallized from methanol, yield 0.3 g. (56%), m.p. 203–210° dec.

Anal. Calcd. for $C_{12}H_{11}NO_3$: C, 66.35; H, 5.11; N, 6.45. Found: C, 66.16; H, 5.22; N, 6.28; λ_{max}, mμ (ϵ) 269 (53,400), 302 (8650); ν_{max} 3300 (m) 1670 (s) 1635 (m), 1612 (m), 1572 (m), and 1550 (m) cm.$^{-1}$.

N,5-Diacetyl-2,α,α-tricarbethoxytryptamine (XXII).—A mixture of 4.25 g. of 5-acetyl-2-carbethoxygramine, 3.2 g. of diethyl acetamidomalonate, 0.3 g. of powdered sodium hydroxide, and 250 ml. of toluene was refluxed until no dimethylamine was detected in the stream of nitrogen bubbling through the reaction medium (*ca.* 25 hr.). The mixture was filtered hot, concentrated *in vacuo* to one half of its original volume, and chilled. The precipitated product was collected on filter and purified for analysis by recrystallization from toluene, m.p. 141–143°, yield 5.5 g. (81%).

Anal. Calcd. for $C_{23}H_{28}N_2O_8$: C, 59.99; H, 6.13; N, 6.08. Found: C, 60.19; H, 5.93; N, 6.05; λ_{max}, mμ (ϵ) 268 (56,700), 311 (9700); ν_{max} 1580 (m), 1610 (m), 1670 broad (s), 1730 broad (s) and 3330 (m) cm.$^{-1}$.

5-Acetyltryptophan (XXIII).—A solution of 7 g. of N,5-diacetyl-2,α,α-tricarbethoxytryptamine in 96 ml. of acetic acid and 24 ml. of 20% hydrochloric acid was refluxed for 8 hr., chilled, and filtered. The filtrate was evaporated *in vacuo* to dryness at temperatures not exceeding 40°. The purple residue was dissolved in ethanol, treated with a small quantity of anhydrous ether, and filtered. This operation was repeated until, upon evaporation of a small portion of the filtrate, a colorless product was obtained. The filtrate was chilled to give 1.25 g. (29%) of crystalline 5-acetyltryptophan hydrochloride, m.p. dec. above 200°.

Anal. Calcd. for $C_{13}H_{14}N_2O_3 \cdot HCl$: C, 55.22; H, 5.35; N, 9.91. Found: C, 55.47; H, 5.38; N, 9.80; λ_{max}, mμ (ϵ) 250.5 (33,000), 295 (8000); ν_{max} 815 (ms), 1493 (ms), 1578 (ms), 1600 (ms), 1639 (s), 1743 (vs), and 3300 (ms) cm.$^{-1}$.

1-Substituted 6-Acetyl-1,2,3,4-tetrahydro-β-carbolines (XXIV–XXIX, Table I). A.—A solution of 0.1 mole of 5-acetyltryptamine hydrochloride and 0.105 mole of phenylacetaldehyde, hydrocinnamaldehyde, *p*-methoxyphenylpyruvic acid, or 3,4-dimethoxyphenylpyruvic acid in 1400 ml. of 1-butanol was refluxed for 3.5–4 hr. (19 hr. for XXVI) and allowed to cool to room temperature. The precipitated product was filtered off, washed with ether, and purified by recrystallization from methanol (XXVIII, XXIX), ethanol (XXVII), or water (XXVI). The base of XXVI was obtained by chloroform extraction of an alkaline solution of the hydrochloride, followed by evaporation of the extracts and recrystallization of the residue from aqueous ethanol.

B.—A solution of 4.35 g. of 5-acetyltryptamine and 2.3 g. of benzaldehyde in 250 ml. of dry benzene was refluxed for 2 hr. with azeotropic removal of water. The reaction mixture was filtered hot and evaporated *in vacuo* to dryness. The yellow residue was dissolved in 160 ml. of ethanol saturated with hydrogen chloride and allowed to stand at room temperature for 1 hr. The precipitate was filtered off and dissolved in water. The aqueous solution was basified with sodium hydroxide and extracted with chloroform. The chloroform extracts were dried over sodium sulfate and evaporated *in vacuo*. The residue was recrystallized from ethanol to give XXV ethanolate. A nonsolvated product was obtained by drying at 140° (0.1 mm.) for 3 hr.

C.—A solution of 6.65 g. of 5-acetyltryptamine in 50 ml. of methanol, 40 ml. of 1*N* sulfuric acid, and 250 ml. of water was treated with 14.5 g. of acetaldehyde. The reaction mixture was kept at 40° for 2.5 hr. and at 90° for 1.5 hr., cooled, made basic with ammonia, and extracted with chloroform. The extracts were dried over sodium sulfate and evaporated *in vacuo*. The residue was crystallized from ethanol. The hydrochloride was obtained by dissolving the base in ethanol, adding excess ethereal

hydrogen chloride, and recrystallizing the precipitated salt from ethanol.

10-Acetyl-17,18-dimethoxy-15,16,17,18,19,20-hexadehydroyohimbane (XXX).—A solution of 5.2 g. of 6-acetyl-1-(3,4-dimethoxybenzyl)-1,2,3,4-tetrahydro-β-carboline hydrochloride in 75 ml. of 37% formaldehyde and 130 ml. of acetic acid was heated on a steam bath for 1 hr., treated with 100 ml. of water, and made basic in the cold with 20% sodium hydroxide solution. The precipitated product was filtered, dissolved in acetonitrile, and passed through a 25-g. Florisil column. Combined eluate and washings were evaporated *in vacuo* and the residue was recrystallized from acetonitrile, yield 50%, m.p. 216–223° dec.

Anal. Calcd. for $C_{23}H_{24}N_2O_3$: C, 73.38; H, 6.42; N, 7.44. Found: C, 73.11; H, 6.68; N, 7.20; λ_{max}, mμ (ε) 257 (46,650), 287 (14,750); ν_{max} 3300 (m), 1660 (s), 1625 (ms), 1592 (m), 1525 (m), 855 (m), and 810 (m) cm.$^{-1}$.

Acknowledgment.—We are indebted to Drs. J. Gylys and M. Osborne for their pharmacological studies. We wish to thank Mr. R. Puchalski for spectral data and Mrs. U. Zeek and Mr. T. Wildeman for analytical determinations.

Investigations in Heterocycles. XV. Methylphenidate: A Versatile Intermediate in the Synthesis of Bicyclic Heterocycles with a Bridgehead Nitrogen Atom

GEORGE DESTEVENS AND MARCEL BERNIER

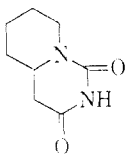
Research Department, CIBA Pharmaceutical Company, Division of CIBA Corporation, Summit, New Jersey

Received September 16, 1963

Methyl α-phenyl-2-piperidineacetate (methylphenidate[1]) has been shown to be a useful intermediate in the synthesis of a variety of compounds related to hexahydro-1H-pyrido[1,2*c*]pyrimidine-1,3-(2H)dione. In addition, this intermediate has been utilized in the synthesis of the novel bicyclo heterocycles hexahydropyrazolo-[1,5*a*]pyridin-2-(1H)one and 4,5,6,7-tetrahydropyrazolo[1,5*a*]pyridin-2-(1H)one.

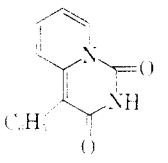
The recent treatise by Mosby[2] on compounds containing bridgehead nitrogen atoms has made evident the tremendous amount of research that has been carried out in this area of heterocyclic chemistry. It was noted particularly that an extensive amount of work has been done in 1H- and 2H-pyridoheterocycles. However, two groups of compounds in this series which have received little attention are the derivatives hexahydro-1H-pyrido[1,2*c*]pyrimidine-1,3(2H)diones and also hexahydro- and 4,5,6,7-tetrahydropyrazolo[1,5*a*]-pyridin-2(1H)ones. Each of these will now be considered separately.

Hexahydro-1H-pyrido[1,2*c*]pyrimidine-1,3-(2H)-diones.—Winterfeld and Göbel[3] reported on the synthesis of the parent substance in this series. They found that urethane readily underwent condensation with methyl 2-piperidineacetate to form I in good yields. Later, the same authors indicated that I could also be synthesized[4] by allowing methyl 2-piperidine acetate dissolved in aqueous hydrochloric acid to react with potassium cyanate. Methylation of I with

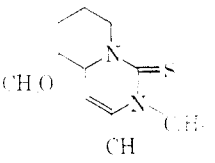


I

diazomethane afforded the corresponding 2-methyl derivative. In the meantime, Hunger and Hoffmann[5] had prepared 1H-4-phenylpyrido[1,2*c*]pyrimidine-1,3-(2H)dione (II) by condensing α-phenyl-α-(2-pyridyl)-acetamide with diethyl carbonate. Finally, Baker and McEvoy[6] produced the pyrido[1,2*c*]pyrimidine (III) through the interaction of 2-(2-oxopropyl)-3-methoxypiperidine with phenyl isothiocyanate. These reports and the availability to us of methyl α-phenyl-2-piperidineacetate (IV) suggested the synthesis of a variety of hexahydro-1H-pyrido[1,2*c*]pyrimidine-1,3-



II



III

(2H)diones and 1-thioxo-3-ones. In addition, it was conceivable that chemical modifications of this biologically active substance might give rise to compounds with different biological effects. The sequence of reactions leading to the hexahydro-1H-pyrido[1,2*c*]-pyrimidine-1,3-(2H)diones and thioxo analogs is shown in Scheme I. The carbamyl and thiocarbamyl intermediates and the bridged nitrogen atom heterocycles prepared in these series are listed in Tables I and II, respectively.

It was found that compound IV readily underwent condensation with alkyl and aryl isocyanates and isothiocyanates to yield the N-substituted carbamoyl and thiocarbamoyl derivatives. These in turn were readily converted to the 2-substituted hexahydro-4-phenyl-1H-pyrido[1,2*c*]pyrimidine-1,3-(2H)diones and 1-thioxo-3-ones in refluxing ethyl alcohol containing hydrogen chloride. It was also possible to obtain the 2-substituted hexahydro-4-phenyl-1-thioxo-1H-pyrido-[1,2*c*]pyrimidine-3-ones merely by heating under reflux an ethyl alcohol solution of the substituted isothio-

(1) Ritalin®.
(2) W. J. Mosby, "Heterocyclic Systems with Bridgehead Nitrogen Atoms," Vol. I and II, Interscience Publishers, Inc., New York, N. Y., 1961.
(3) K. Winterfeld and W. Göbel, *Chem. Ber.*, **89**, 1642 (1956).
(4) K. Winterfeld and W. Göbel, *ibid.*, **92**, 637 (1959).
(5) A. Hunger and K. Hoffmann, *Helv. Chim. Acta*, **40**, 1319 (1957).
(6) B. R. Baker and F. McEvoy, *J. Org. Chem.*, **20**, 136 (1955).