and 2 g. of ammonium acetate at 95–100°, diluted with 50–60 ml. of methanol, and cooled, yielding 5.6 g. (80%) of orange-red needles, m.p. 229–230°. An analytical sample was sublimed at 0.5 mm.

Anal. Calcd. for $C_{11}H_9FN_2O_2$: C, 59.99; H, 4.12; F, 8.63; N, 12.73. Found: C, 60.23; H, 4.18; F, 8.65; N, 12.90.

6-Fluoro-α-methyltryptamine.—A solution of 5.6 g. of 6-fluoro-3-(2-methyl-2-nitrovinyl)indole in 100 ml. of tetrahydrofuran was added dropwise to 6.5 g. of lithium aluminum hydride in 150 ml. of tetrahydrofuran and refluxed for 2 hr. After the usual procedure, 3.0 g. (61%) of crystals were obtained, m.p. 102–105° (ethyl acetate–petroleum ether). An analytical sample was recrystallized from ethyl acetate, m.p. 104–106°.

Anal. Calcd. for $C_{11}H_{13}FN_2$: C, 68.73; H, 6.82; N, 14.57. Found: C, 68.39; H, 6.83; N, 14.22.

The **picrate,** red crystals from methanol–water, changed to orange-yellow when heated above 100–110°; m.p. 232–233° dec.

Anal. Calcd. for $C_{17}H_{16}FN_5O_7$: C, 48.46; H, 3.83; N, 16.63. Found: C, 49.03; H, 4.28; N, 16.77.

5-Fluoro-3-indolealdehyde.—A solution of 7.7 g. of 5-fluoroindole[6] added to 5.8 ml. of phosphorus oxychloride in 20 ml. of dimethylformamide, and processed as described for the 6-fluoro analog, afforded 7.5 g. (80%) of crystals, m.p. 170–171°.

Anal. Calcd. for C_9H_6FNO: C, 66.25; H, 3.71; F, 11.65. Found: C, 66.76; H, 4.22; F, 11.60.

5-Fluoro-3-(2-methyl-2-nitrovinyl)indole.—Reaction between 7.3 g. of 5-fluoro-3-indolealdehyde and 20 ml. of nitroethane in the presence of 2.3 g. of ammonium acetate, carried out as described in preceding sections, gave 6.1 g. (62%) of orange crystals, m.p. 186–186.5° (from methanol).

Anal. Calcd. for $C_{11}H_9FN_2O_2$: C, 59.99; H, 4.12; N, 12.73. Found: C, 60.25; H, 3.89; N, 12.45.

5-Fluoro-α-methyltryptamine.—The foregoing compound (5.8 g.), reduced exactly as described for the 6-fluoro isomer, was precipitated from an etheral solution as the hydrochloride, m.p. 228–230°; yield 4.9 g. (81%). An analytical sample was purified from toluene–ethanol; m.p. 233–234°.

Anal. Calcd. for $C_{11}H_{14}ClFN_2$: C, 57.77; H, 6.17; F, 8.31; N, 12.25. Found: C, 57.79; H, 6.48; F, 8.29; N, 12.27.

The yellow crystalline **picrate,** from methanol–water, melted at 234–235° dec.

Anal. Calcd. for $C_{17}H_{16}FN_5O_7$: C, 48.46; H, 3.83; F, 4.51; N, 16.63; Found: C, 48.73; H, 3.79; F, 3.99; N, 17.07.

Acknowledgment.—We are indebted to Mr. H. G. McCann of the Microanalytical Laboratory, National Institute of Arthritis and Metabolic Diseases, for analyses.

Acyltryptamines. II. Synthesis of Acyltryptamines, Indazoles, and Azepinoindoles from the Acylphenylhydrazones of 2,3-Piperidinedione[1]

MAXIMILIAN VON STRANDTMANN, MARVIN P. COHEN, AND JOHN SHAVEL, JR.

Warner-Lambert Research Institute, Morris Plains, New Jersey

Received March 25, 1963

The 3-(*o*-, *m*-, and *p*-acylphenyl)hydrazones of 2,3-piperidinedione (I) were prepared by the Japp–Klingemann coupling of the corresponding acylbenzenediazonium salts with 2-oxo-3-piperidinecarboxylic acid. The acyl substituents were *o*-, *m*-, and *p*-acetyl, *o*-, *m*-, and *p*-benzoyl, *p*-propionyl, *p*-isonicotinoyl, and *p*-(4-chlorobenzoyl). The Fischer-indole cyclization of the *p*-acylphenylhydrazones gave 6-acyl-1,2,3,4-tetrahydro-1-oxo-β-carbolines (II) which on hydrolysis and decarboxylation yielded 5-acyltryptamines (IV). Cyclizations of the *m*-acylphenylhydrazones gave a mixture of 5- and 7-acyl-1,2,3,4-tetrahydro-1-oxo-β-carbolines (VI, V) which on hydrolysis and decarboxylation yielded azepino[5,4,3-*cd*]indoles (X) and 6-acyltryptamines (VIII), respectively. The *o*-acylphenylhydrazones on cyclization gave 3-methyl-2-(1,2,5,6-tetrahydro-2-oxo-3-pyridyl)-2H-indazole and 3-phenyl-2-(1,2,5,6-tetrahydro-2-oxo-3-pyridyl)-2H-indazole. These were reduced catalytically to the 3-methyl-2-(2-oxo-3-piperidyl)-2H-indazoles and 3-phenyl-2-(2-oxo-3-piperidyl)-2H-indazoles (XIII). Hydrolysis of the indazoles gave the corresponding derivatives of 5-amino-2-indazolylpentanoic acid (XV, XVI). The 5-acyltryptamines showed antiserotonin and hypotensive properties. The most active compound, 5-acetyltryptamine, which produced marked hypotensive effect in the anesthetized and unanesthetized dog, failed to elicit the same response in man when tested in the clinic.

The synthesis of tryptamines has been extensively pursued because of the biological activities of many naturally occurring substances containing this moiety. As a result of our investigations on the chemical modifications of indole alkaloids it became apparent to us that tryptamines, substituted in the benzene ring by acyl groups, had not previously been prepared. During the course of our synthesis in this area we encountered some interesting chemical and pharmacological findings which prompted us to expand our research to include indazoles and azepinoindoles.

The most feasible synthetic scheme appeared to be that utilized by Abramovitch and Shapiro[2] where substituted benzenediazonium salts are coupled with 3-carboxy-2-piperidone to give hydrazones which are cyclized to 1,2,3,4-tetrahydro-1-oxo-β-carbolines. Ring opening of the oxocarbolines followed by decarboxylation of the resulting 2-carboxytryptamines yields the tryptamines.[3]

Coupling of the *o*-, *m*-, and *p*-acylbenzenediazonium salts with 3-carboxy-2-piperidone gave the corresponding 3-(*o*-, *m*-, and *p*-acylphenyl)hydrazones of 2,3-piperidinedione Ia–i (Table I). Cyclization of the (*p*-acylphenyl)hydrazones of 2,3-piperidinedione Ia–d in refluxing 88% formic acid gave the 6-acyl-1,2,3,4-tetrahydro-1-oxo-β-carbolines (IIa–d, Table II). Hydrazone Ie, which resisted cyclization by formic acid, was successfully cyclized by polyphosphoric acid. Base-catalyzed hydrolysis of IIa–e gave the corresponding 5-acyl-2-carboxytryptamines (IIIa–e, Table III) which were decarboxylated in refluxing hydrochloric acid to the 5-acyltryptamines (IVa–e, Table IV).

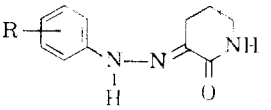
(1) Presented in part as a Communication to the Editor, *J. Am. Chem. Soc.*, **84**, 881 (1962), and before the Division of Medicinal Chemistry at the 141st National Meeting of the American Chemical Society, Washington, D. C., March 26, 1962.

(2) R. A. Abramovitch and D. Shapiro, *Chem. Ind.* (London), 1255 (1955); *J. Chem. Soc.*, 4589 (1956).

(3) S. Keimatsu, S. Sugasawa, and G. Kasuya, *J. Pharm Soc. Japan*, **48**, 762 (1928).

TABLE I

PHENYLHYDRAZONES OF 2,3-PIPERIDINEDIONE

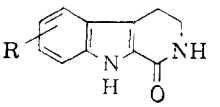


Compound	R	M.p., °C.	Yield, %	Formula	Calcd., % (Found, %) C	H	N	λ_{max}^{EtOH}, mμ (ε)
Ia	*p*-CH_3CO	231–233	82	$C_{12}H_{13}N_3O_2$	63.66 (63.40)	6.16 (6.28)	17.13 (16.93)	238 (10,800); 351 (42,000)
Ib	*p*-C_2H_5CO	218–221	58	$C_{14}H_{17}N_3O_2$	64.84 (64.55)	6.61 (6.72)	16.21 (16.19)	235 (14,950); 347 (42, 400)
Ic	*p*-C_6H_5CO	208–210	55	$C_{18}H_{17}N_3O_2$	70.34 (70.06)	5.58 (5.88)	13.67 (13.50)	245 (16,450); 360 (40,200)
Id[a]	*p*-Cl-C_6H_4-CO	233–235	73	$C_{18}H_{16}ClN_3O_2 \cdot 0.5C_2H_5OH$	62.55 (62.56)	5.24 (4.97)	11.52 (11.41)	250 (17,700); 361 (40,600)
Ie	*p*-N-C_5H_4-CO	229–230	50	$C_{17}H_{16}N_4O_2$	66.22 (66.06)	5.23 (5.39)	18.17 (18.34)	235 (10,050); 271 (6250) 365 (39,650)
If	*m*-CH_3CO	206–208	41	$C_{13}H_{15}N_3O_2 \cdot 0.5H_2O$	61.40 (61.58)	6.34 (6.59)	16.53 (16.87)	233 (19,500); 312.5 (21,200)
Ig	*m*-C_6H_5CO	222–225	50	$C_{18}H_{17}N_3O_2 \cdot 0.5H_2O$	68.33 (68.07)	5.73 (5.57)	13.28 (13.18)	245 (23,500); 314 (26,000)
Ih	*o*-CH_3CO	233–235	29	$C_{13}H_{15}N_3O_2$	63.66 (63.90)	6.16 (6.42)	17.13 (17.15)	230 (17,300); 254 (14,700) 312 (14,700); 369 (13,200)
Ii	*o*-C_6H_5CO	227–229	95	$C_{18}H_{17}N_3O_2$	70.34 (70.06)	5.58 (5.88)	13.67 (13.50)	232 (15,000); 258 (14,000) 313 (14,700); 384 (9700)
XIIa	*o*-CH_3CHOH	235–237	36	$C_{13}H_{17}N_3O_2$	63.14 (63.37)	6.43 (6.70)	16.99 (17.20)	232 (11,800); 326 (22,000)
XIIb	*o*-C_6H_5CHOH	251–252	56	$C_{18}H_{19}N_3O_2$	69.88 (70.08)	6.19 (6.01)	13.58 (13.38)	231 sh (12,000); 326 (22,000)

[a] Cl, Calcd.: 9.72; Found: 9.77.

TABLE II

1,2,3,4-TETRAHYDRO-1-OXO-β-CARBOLINES

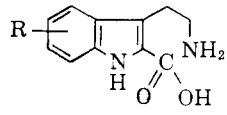


Compound	R	M.p., °C.	Yield, %	Formula	Calcd., % (Found, %) C	H	N	λ_{max}^{EtOH}, mμ (ε)
IIa	6-CH_3CO	373–375	78	$C_{13}H_{12}N_2O_2$	68.40 (68.35)	5.30 (5.33)	12.27 (12.08)	273 (42,250) 298–305 (sh) (8800)
IIb	6-C_2H_5CO	359–363	90	$C_{14}H_{14}N_2O_2$	69.40 (69.00)	5.82 (5.97)	11.56 (11.28)	272 (43,600) 306 (8100)
IIc	6-C_6H_5CO	286.5–289.5	92	$C_{18}H_{14}N_2O_2$	74.46 (74.59)	4.86 (4.92)	9.65 (9.61)	282 (37,300)
IId[a]	6-(Cl-C_6H_4-CO)	280.5–282.5	69	$C_{18}H_{13}ClN_2O_2$	66.57 (66.45)	4.03 (4.19)	8.63 (8.83)	216 (21,800) 242 (19,800) 284 (38,800)
IIe	6-(N-C_5H_4-CO)	383–388	80	$C_{17}H_{13}N_3O_2$	70.09 (70.23)	4.50 (4.72)	14.43 (14.20)	260 (30,000) 285 (20,200)
Va	7-CH_3CO	285.5–288.5	60	$C_{13}H_{12}N_2O_2$	68.40 (68.30)	5.30 (5.38)	12.27 (12.45)	248 (27,100) 315 (23,700) 227 (12,000)
Vb	7-C_6H_5CO	250–252	52	$C_{18}H_{14}N_2O_2$	74.47 (74.49)	4.86 (5.03)	9.65 (9.45)	250 (12,050) 312 (11,400) 223 (24,500)
VIa	5-CH_3CO	243–245	20	$C_{13}H_{12}N_2O_2$	68.40 (68.62)	5.30 (5.48)	12.27 (12.05)	258 (41,800) 227 (10,080) 229 (25,200)
VIb	5-C_6H_5CO	124.5–131.5	37	$C_{18}H_{14}N_2O_2 \cdot C_2H_5OH$	71.40 (71.64)	5.99 (5.78)	8.33 (8.50)	242 (23,000) 322 (9700)

[a] Cl, Calcd.: 10.92; Found: 10.97.

The cyclization of the *m*-acylphenylhydrazones of 2,3-piperidinedione (If,g) gave mixtures of 7-acyl-1,2,3,4-tetrahydro-1-oxo-β-carbolines (Va,b, Table II) and 5-acyl-1,2,3,4-tetrahydro-1-oxo-β-carbolines (VIa,b, Table II) in approximately 3:1 ratios. These isomers were separated by fractional crystallization from ethanol. The 7-benzoyl and 7-acetyl derivatives had absorption bands in the 800 and 890 cm.$^{-1}$ regions which are attributed to aromatic 1,2,4-trisubstitution. The 5-benzoyl isomer had no significant bands in the

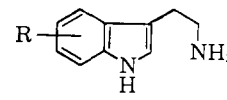
TABLE III
2-CARBETHOXYTRYPTAMINES



Compound	R	M.p., °C.	Yield, %	Formula	Calcd., % (Found, %) C	H	N	Cl	λ_{max}^{EtOH}, mμ (ε)
IIIa	5-CH_3CO	340–346[a]	93	$C_{13}H_{14}N_2O_3 \cdot H_2O$	59.08 (59.04)	6.10 (6.18)	10.60 (10.77)		266.5 (47,000); 303 (8000)
		363		$C_{13}H_{14}N_2O_3 \cdot HCl$	55.22 (55.51)	5.35 (5.62)	9.91 (9.67)	12.54 (12.51)	266 (51,700); 303 (8900)
IIIb	5-C_2H_5CO	271.5–275.5	93	$C_{14}H_{16}N_2O_3$	64.60 (64.46)	6.20 (6.19)	10.76 (10.76)		265 (49,000); 304 (8200)
		301.5–307.5		$C_{14}H_{16}N_2O_3 \cdot HCl$	56.66 (56.74)	5.78 (5.98)	9.44 (9.71)	11.95 (12.08)	266 (51,500); 304 (9100)
IIIc	5-C_6H_5CO	287.5–293.5[b]	90	$C_{18}H_{16}N_2O_3$	70.11 (70.38)	5.23 (5.28)	9.09 (9.33)		276 (37,000); 296–305 (10,100)
		270–272		$C_{18}H_{16}N_2O_3 \cdot HCl$	62.70 (62.93)	4.97 (5.05)	8.12 (7.97)	10.22 (10.24)	277 (41,200)
IIId	5-(Cl-C6H4-CO)	268–270	95	$C_{18}H_{15}ClN_2O_3$	63.07 (63.33)	4.41 (4.57)	8.17 (7.93)	10.34 (10.09)	297.5 (37,500)
IIIe	5-(N-C5H4-CO)	343–353	80	$C_{17}H_{15}N_3O_2 \cdot 0.5C_2H_5OH$	65.04 (64.83)	5.46 (5.80)	12.64 (12.78)		238 (24,200); 277 (31,000); 311–319 (10,100)
VIIa	6-CH_3CO	242–245	90	$C_{13}H_{14}N_2O_3 \cdot H_2O \cdot 0.5C_2H_5OH$	58.52 (58.74)	6.66 (6.40)	9.75 (9.73)		248 (24,000); 308 (21,600)
		272.5–280.5		$C_{13}H_{14}N_2O_3 \cdot HCl$	51.91 (52.07)	5.70 (5.91)	9.31 (9.28)	11.79 (11.89)	
VIIb	6-C_6H_5CO	210–213	96	$C_{18}H_{16}N_2O_3 \cdot 0.5H_2O$	68.13 (68.19)	5.40 (5.26)	8.82 (8.58)		226 (26,000); 249 (19,600); 313 (18,000)
IXa	4-CH_3CO	317–320	93	$C_{13}H_{14}N_2O_3$	63.40 (63.59)	5.73 (5.99)	11.38 (11.46)		216 (30,000);243(sh)(13,500) 260 (15,000); 353 (5,300) 418 (6,700)
IXb	4-C_6H_5CO	242–252	88	$C_{18}H_{16}N_2O_3 \cdot 0.5C_2H_5OH$	68.86 (69.14)	5.78 (5.80)	8.45 (8.41)		230 (25,600); 267 (15,200) 362 (5,500); 443 (7,500)

[a] At 270° softens, puffs up, and resolidifies. [b] Melts at 240–243° and resolidifies.

TABLE IV
TRYPTAMINES



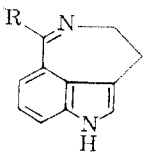
Compound	R	M.p., °C.	Yield, %	Formula	Calcd., % (Found, %) C	H	N	Cl	λ_{max}^{EtOH}, mμ (ε)
IVa	5-CH_3CO	140.5–142.5	57	$C_{12}H_{14}N_2O$	71.26 (70.99)	6.98 (6.93)	13.85 (14.09)		254 (34,400); 299 (pl) (7850)
		230–232		$C_{12}H_{14}N_2O \cdot HCl$	60.37 (60.48)	6.33 (6.37)	11.74 (11.51)	14.87 (14.88)	252 (33,400); 297 (7350)
IVb	5-C_2H_5CO	127.5–130.5	26	$C_{13}H_{16}N_2O$	72.19 (71.91)	7.46 (7.46)	12.95 (12.92)		253 (34,400); 297 (7200)
		214–216		$C_{13}H_{16}N_2O \cdot HCl$	61.77 (61.96)	6.78 (6.79)	11.08 (11.12)	14.03 (14.05)	252 (35,600); 297 (7400)
IVc	5-C_6H_5CO	236–238	50	$C_{17}H_{16}N_2O \cdot HCl$	67.88 (67.83)	5.70 (5.85)	9.31 (9.60)	11.79 (11.53)	220 (21,600); 262.5 (25,000) 306 (9600)
IVd	5-(Cl-C6H4-CO)	264–267	26	$C_{17}H_{15}ClN_2O \cdot HCl$	60.90 (61.13)	4.81 (4.76)	8.36 (8.63)	21.15 (20.92)	219 (23,300); 265 (26,700) 308 (10,150)
IVe	5-(N-C5H4-CO)	251–256	57	$C_{16}H_{15}N_3O \cdot 2HCl$	56.81 (56.88)	5.07 (5.36)	12.42 (12.18)	20.97 (20.80)	232 (25,400); 266 (18,500) 311 (9500)
VIIIa	6-CH_3CO	148.5–150.5	14	$C_{12}H_{14}N_2O$	71.26 (71.38)	6.98 (7.18)	13.85 (14.08)		237 (sh) (15,300); 253 (21,400) 301 (12,900); 335 (7000)
VIIIb	6-C_6H_5CO	249–251	17	$C_{17}H_{16}N_2O \cdot 0.5C_2H_5OH \cdot HCl$	66.76 (66.56)	6.23 (6.26)	8.65 (8.94)	10.95 (11.06)	219 (27,900); 254 (18,700); 306 (12,690)

800–900 cm.$^{-1}$ region whereas the 5-acetyl isomer showed one band at 870 cm.$^{-1}$. The 7-acyl-1,2,3,4-tetrahydro-1-oxo-β-carbolines (Va,b) were hydrolyzed by alkali to the 6-acyl-2-carboxytryptamines(VIIa, b, Table III) which were then decarboxylated in refluxing hydrochloric acid to 6-acyltryptamines (VIIIa,b, Table IV).

The 5-acyl-1,2,3,4-tetrahydro-1-oxo-β-carbolines (VIa,b) were hydrolyzed to 4-acyl-2-carboxytryptamines(IXa,b, Table III), which on acid decarboxyla-

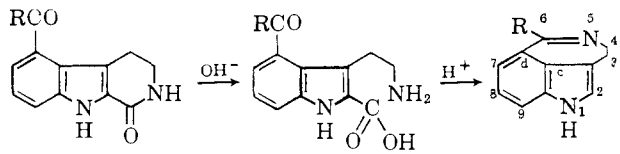
TABLE V

AZEPINO[5,4,3-*cd*]INDOLES



Compound	R	M.p., °C.	Yield, %	Formula	Calcd., % (Found, %) C	H	N	$\lambda_{max}^{CHCl_3}$, mμ (ε)
Xa	CH_3	274.5-279.5	53	$C_{12}H_{12}N_2$	78.22 (77.98)	6.57 (6.59)	15.21 (15.36)	241 (18,250); 343 (4450); 418 (1300)
Xb	C_6H_5	174-176	14	$C_{17}H_{14}N_2$	82.90 (83.18)	5.73 (6.02)	11.37 (11.15)	237.5 (17,600); 287 (240); 317 (4800)

tion gave compounds lacking carbonyl absorption in the infrared.



VI IX X

a, R = CH_3; b, R = C_6H_5

It was apparent that the primary amine of the side chain reacted with the carbonyl group to give derivatives of the novel ring structure, 1H-azepino[5,4,3-*cd*]-indole (Xa,b,[4] Table V). Rast molecular weight determination confirmed the monomeric empirical formula.

The reactions described proceeded with good yields except for the decarboxylation step which was generally a slow process governed by the electron-withdrawing properties of the substituent. We have observed that the ease of decarboxylation decreases with the increasing electronegativity of the substituent *para* to the ring nitrogen, in agreement with Abramovitch's[5] assumption that protonation of the indole nitrogen is the rate-determing step of this reaction. Generally, the 5-alkanoyl-2-carboxytryptamines were decarboxylated faster than the corresponding aroyl derivatives. The 4- and 6-benzoyl-2-carboxytryptamines, both of which have the substituent *meta* to the indole nitrogen, were decarboxylated more rapidly than 5-benzoyl-2-carboxytryptamine. In some cases, extensive decomposition of the product was minimized by isolation of the tryptamine prior to the completion of the reaction and recyclization of the recovered amino acid hydrochloride. Efforts to improve this step by using resorcinol or dimethylaniline[6] as decarboxylating agents were fruitless.[7]

The cyclization of the *o*-acylphenylhydrazones of 2,3-piperidinedione (Ih,i) gave basic substances whose analytical and spectral data were incompatible with the structure of the desired 8-acyl-1,2,3,4-tetrahydro-1-oxo-β-carbolines. The high nitrogen content of the products indicated that cyclization to the indazolyl-tetrahydropyridones (XIa,b, Table VI) had taken place. This cyclization is believed to proceed *via* the nucleophilic attack of the basic nitrogen of the ene-hydrazine form[9] of the hydrazone on the carbonyl carbon, followed by realignment of bonds and elimination of the elements of water (Chart I). One of the by-products obtained was 3-methylindazole[10] which was presumably formed by intramolecular condensation of the hydrazine resulting from the hydrolysis of the hydrazone. This was avoided by the use of glacial acetic acid instead of 88% formic acid as the cyclizing agent. In an effort to circumvent the formation of indazoles, the *o*-acylanilines were reduced prior to diazotization and coupling. Nevertheless, the cyclization of the resulting *o*-(α-hydroxyethyl)phenylhydrazone of 2,3-piperidinedione XIIa (Table I) and of the corresponding α-hydroxybenzyl analog XIIb yielded indazolylpiperidones (XIIIa,b, Table VI) which were identical with those obtained by catalytic reduction of the indazolyltetrahydropyridones XIa,b. This can be rationalized by assuming a nucleophilic attack of the more basic nitrogen of the azo form[9] of the hydrazone XII on the carbonium ion followed by a realignment of bonds[11] (Chart I).

Of interest is the comparison of the ultraviolet spectrum of 2,3-dimethylindazole[10] with those of XIII and XIa (Fig 1). The most characteristic feature of all the indazole derivatives investigated in the course of this work was the strong maximum in the 210 mμ region. This absorption was not described in previous studies of the ultraviolet spectra of indazoles.[12] The similarity of the ultraviolet spectrum of 2,3-dimethylindazole with that of XIIIa prompted us to formulate XIIIa,b as 3-methyl-(or 3-phenyl-) -2-(2-oxo-3-piperidyl)-2H-indazole rather than as 2,3-dihydro-3-methyl- (or 3-phenyl-) -2-(1,2,5,6-tetrahydro-2-oxo-3-pyridyl)-1H-indazole (XIVa,b). The formation of XIVa,b might have been anticipated from the cyclization of the ene-hydrazine form of XIIIa,b as well as from the rather unlikely reduction of the pyrazole ring of XIa,b.

(4) 3,4-Dihydro-6-methyl-1H-azepino[5,4,3-*cd*]indole (Xa) and 3,4-dihydro-6-phenyl-1H-azepino[5,4,3-*cd*]indole (Xb).

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

(6) H. Plieninger, *Chem. Ber.*, **83**, 268 (1950).

(7) Similar results were obtained by Abramovitch (see ref. 5) in the attempted decarboxylation of 5-nitro-2-carboxytryptamine and 5-chloro-2-carboxytryptamine with copper or its salts in quinoline. When heated with resorcinol or glycerol the compounds recyclized.

(8) 3-Methyl-2-(1,2,5,6-tetrahydro-2-oxo-3-pyridyl)-2H-indazole (XIa) and 3-phenyl-2-(1,2,5,6-tetrahydro-2-oxo-3-pyridyl)-2H-indazole (XIb).

(9) For a recent discussion of the tautomeric forms of hydrazones see R. O'Connor, *J. Org. Chem.*, **26**, 4375 (1961).

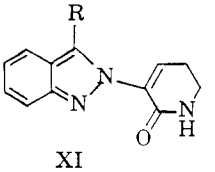
(10) (a) E. Fischer and H. Kuzel, *Ann.*, **211**, 261 (1883); (b) E. Fischer and J. Tafel, *ibid.*, **227**, 303 (1885).

(11) The cyclization of *o*-phenylazobenzyl alcohol to 2-phenylindazole has been reported by P. Freundler, *Compt. Rend.*, **136**, 1136 (1903); **138**, 1276 (1904).

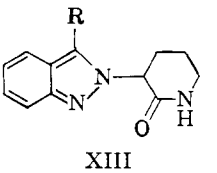
(12) (a) J. Derkosch, O. E. Polansky, E. Rieger, and G. Derflinger, *Monatsh. Chem.*, **92**, 113 (1961); (b) P. Ramart-Lucas, *Bull. Soc. Chim. France*, **17**, 317 (1950); (c) C. Ainsworth, *J. Am. Chem. Soc.*, **80**, 967 (1958); (d) V. Rousseau and H. B. Lindwall, *ibid.*, **72**, 3047 (1952).

TABLE VI

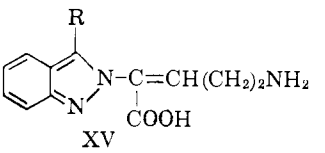
2H-INDAZOLES



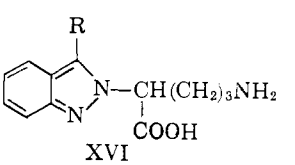
XI



XIII



XV



XVI

Compound	R	M.p., °C.	Yield, %	Formula	Calcd., % (Found, %) C	H	N	λ_{max}^{EtOH}, mμ (ε)
XIa	CH_3	189–192	55	$C_{13}H_{13}N_3O$	68.70 (68.50)	5.76 (5.92)	18.49 (18.29)	212.5 (43,250); 273 (7100); 294 (6500)
XIb	C_6H_5	233–238	70	$C_{18}H_{15}N_3O$	74.72 (74.43)	5.22 (5.44)	14.32 (14.54)	209 (34,900); 311 (11,000)
XIIIa	CH_3	258–260	40	$C_{13}H_{15}N_3O$	68.10 (68.12)	6.59 (6.72)	18.33 (18.20)	212 (45,400); 278 (5,500); 304 (6,500)
XIIIb	C_6H_5	195–197	44	$C_{18}H_{17}N_3O$	74.20 (74.29)	5.88 (5.98)	14.42 (14.64)	208 (42,400); 261 (6,600); 308 (11,00)
XVa	CH_3	223–226	75	$C_{13}H_{15}N_3O_2$	63.66 (63.69)	6.16 (6.30)	17.13 (16.91)	214 (35,100); 279 (5,300); 304 (5,400)
XVb	C_6H_5	272.5–274.5	75	$C_{18}H_{17}N_3O_2$	70.34 (70.04)	5.58 (5.75)	13.67 (13.81)	314 (11,050)
		149.5–157.5	75	$C_{18}H_{17}N_3O_2 \cdot HCl \cdot 0.5H_2O$	61.27 (61.05)	5.43 (5.60)	11.91 (11.77)	314 (10,800)
XVI	C_6H_5	167–170	95	$C_{18}H_{19}N_3O_2 \cdot H_2O$	66.03 (66.23)	6.47 (6.70)	12.84 (12.62)	264 (6,250); 309 (10,300)

Structure XIIIa,b was further supported by the finding that 2,3-dimethylindazole could not be reduced to the corresponding indazoline under the conditions of the conversion of XI to XIII. The infrared spectra of the indazolyltetrahydropyridones XIa,b and the indazolylpiperidones XIIIa,b displayed strong absorption bands in the 1680–1690 cm.$^{-1}$ region. This high frequency of the amide absorption can be attributed to the electron-withdrawing effect of the neighboring indazolyl moiety. Both the saturated and the unsaturated lactams were easily hydrolyzed with acid or base to the corresponding derivatives of 5-amino-2-indazolylpentanoic acid XVa,b, and XVI[13] (Table VI). In accordance with their amino acid structure, XVa,b and XVI displayed a carboxylate band at 1650 cm.$^{-1}$ whereas their hydrochlorides had a carboxyl band at 1725 cm.$^{-1}$. When the aforementioned catalytic hydrogenation of XIa to XIIIa was not interrupted after the uptake of one mole of hydrogen, further reduction, at a much slower rate, took place with the formation of 3-(*o*-ethylphenylhydrazo)-2-piperidone (XVII). That the latter no longer possessed the indazole structure was shown by its ultraviolet spectrum which displayed maxima at 197 (ε 13,050) and 232 mμ (ε 6,200). Evidence that fission of the N-2, C-3 bond had occurred rather than cleavage of the N–N linkage was obtained by a negative β-naphthol test for aromatic amines.[14] Fission of the N–N bond was observed in the course of the subsequent lithium aluminum hydride reduction of XVII to 3-(*o*-ethylphenylhydrazo)-piperidine (XVIII) when a not characterized, oily by-product giving a positive β-naphthol test was also obtained. Similarly the reduc-

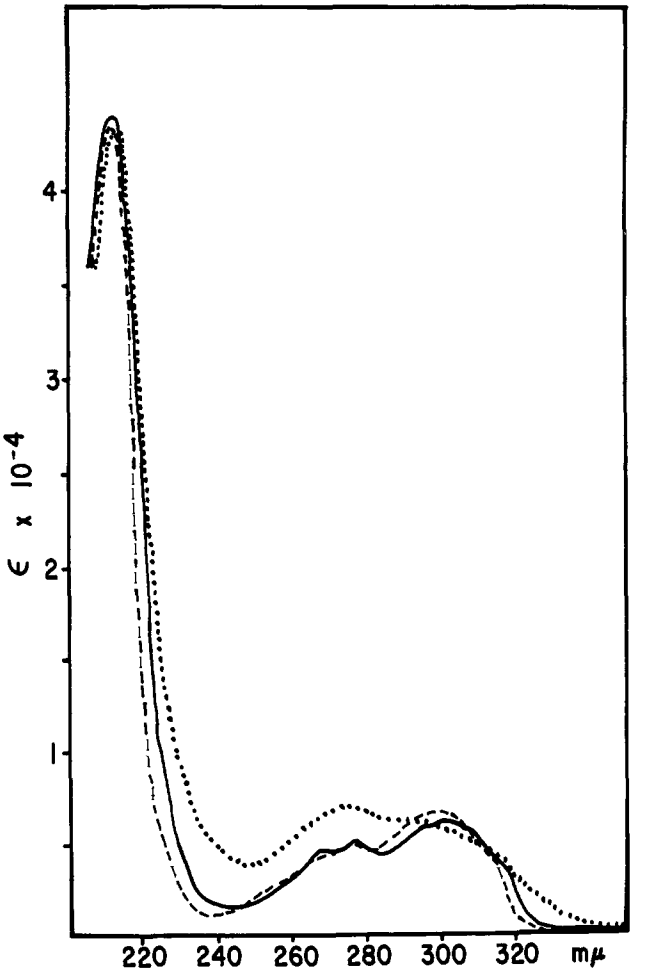
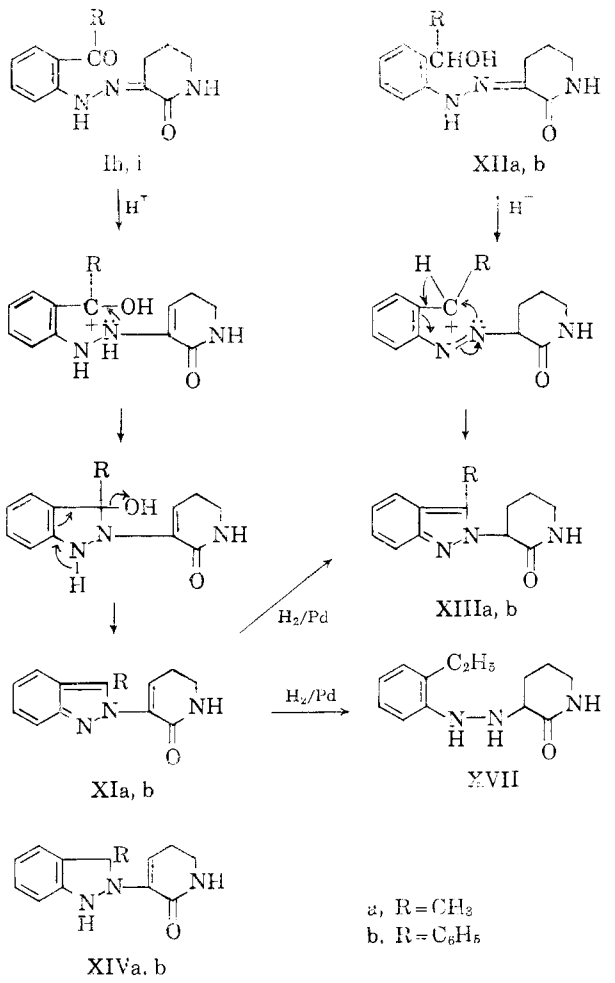


Fig. 1.—The ultraviolet spectra of 2,3-dimethylindazole (– – – –), 3-methyl-2-(2-oxo-3-piperidyl)-2H-indazole (———), and 3-methyl-2-(1,2,5,6-tetrahydro-2-oxo-3-pyridyl)-2H-indazole (. . . .).

(13) 5-Amino-2-(3-methyl-2H-indazole-2-yl)-2-pentenoic acid (XVa), 5-amino-2-(3-phenyl-2H-indazole-2-yl)-2-pentenoic acid (XVb), 5-amino-2-(3-phenyl-2H-indazole-2-yl)-pentanoic acid (XVI).

(14) Reductive cleavage of 2-phenylindazole with sodium and alcohol to give N-(*o*-aminobenzyl)-aniline was observed by K. von Auwers and P. Strodter, *Ber.*, **59**, 529 (1926).

CHART I



tion of XIb with zinc in a mixture of acetic acid and hydrochloric acid gave *o*-benzylaniline which was isolated predominately in the N-acetylated form.[15] The identity of this material was established by comparison with an authentic sample.[16]

Summary of Pharmacological Data.—In the preliminary acute toxicity behavioral screen in mice, the acyltryptamines (Table IV) and the indazoles (Table VI) failed to produce any significant pharmacological effects. Both types were relatively nontoxic, having oral ALD_{50} in the region of 1 g./kg. or greater. The azepinoindoles Xa,b (Table V) induced clonic-tonic convulsions and Straub tail suggestive of central excitation. They were also characterized by higher toxicities, having ALD_{50} of 75 mg./kg. and 400 mg./kg., respectively.

The antiserotonin activity of the acyltryptamines and the azepinoindoles was determined by the method of Woolley,[17] which is based on the prevention of diarrhea induced by administration of 5-hydroxytryptophan, and is summarized as follows (ED_{50}, mg./kg. i.p.): BAS (1-benzyl-2,5-dimethylserotonin), 25; IVa, 10; IVb, 35; IVc, 10; IVd, 15; IVe, 35; VIIIa, 50; VIIIb, 25; Xa, >20; Xb, 50.

(15) An example of N-acetylation in the course of a reduction with zinc in acetic acid of an *o*-aminobenzophenone derivative is described by P. Ruggli and B. Hegedüs, *Helv. Chim. Acta*, **24**, 703 (1941).

(16) (a) O. Fischer and H. Schütte, *Ber.*, **26**, 3085 (1893); (b) C. L. Hewett, L. J. Lermit, H. T. Openshaw, A. R. Todd, A. H. Williams, and R. N. Woodward, *J. Chem. Soc.*, 292 (1948).

(17) D. W. Woolley, *Proc. Soc. Exptl. Biol. Med.*, **93**, 367 (1956).

The cardiovascular effects of the acyltryptamines were examined in mongrel dogs anesthetized with sodium barbital (300 mg./kg.) or sodium pentobarbital (120–180 mg./kg.). Carotid blood pressure was recorded with a mercury manometer and a kymograph. Control blood pressure responses were obtained by i.v. administration of standard reference agents. Right carotid artery occlusion was accomplished by blocking the artery for 45 sec.

The most potent compound was 5-acetyltryptamine (IVa) which produced a depressor response of 39 mm. at 0.025 mg./kg. i.v. A dose of 0.25 mg./kg. caused a fall in blood pressure of 61 mm. that required 25 min. to return to normal. Doses up to 5 mg./kg. did not markedly enhance the hypotensive effect; however, its duration was extended to over 1 hr.

Following administration of 5-acetyltryptamine at all doses, the blood pressure responses to the standard reference agents, such as epinephrine, norepinephrine, acetylcholine, histamine, 1,1-dimethyl-4-phenylpiperazinium iodide, and serotonin and to carotid artery occlusion were either unchanged or only slightly altered, indicating that the drug has no autonomic activity.

The cardiovascular effects of 5-acetyltryptamine were further evaluated in untrained, unanesthetized dogs. Femoral artery blood pressures were recorded with a P 23 Statham pressure transducer and a Grass Model No. 5 polygraph. Oral administration of the drug caused an average 20/20 decrease in the systolic and diastolic blood pressure for 3–4 hr. while leaving the heart rate unaffected. Further pharmacological evaluation of this compound led to its selection for a preliminary clinical trial where it failed to elicit the same response as found in the laboratory.

The hypotensive activity of 5-acyltryptamines decreased with the increase in size of the acyl group. For example, while 5-propionyltryptamine at 2.5–5 mg./kg. produced an effect comparable to 5-acetyltryptamine, only a moderate drop in blood pressure of 20–40 mm. could be obtained by the administration of 10 mg./kg. of isonicotinoyltryptamine (IVc). 5-Benzoyltryptamine (IVe) at 1–5 mg./kg. produced a weak depressor response of less than 20 mm. which lasted less than 10 min., and 5-*p*-chlorobenzoyltryptamine (IVd) was completely inactive.

The hypotensive properties appeared to be limited to the 5-acyltryptamine class, whereas 6-acetyltryptamine (VIIIa) and the cycloanhydro derivative of 4-acetyltryptamine(Xa) produced hypertensive effects. At doses of 0.1–5 mg./kg. azepinoindole(Xa) caused a rise in blood pressure of 5–20 mm., which gradually returned to normal value within 30–60 min. depending on the amount of administered drug. At the same levels VIIIa gave a strong dose dependent depressor response of 10–130 mm. which lasted 12–20 min. The cardiovascular effects of VIIIb and Xb were not evaluated.

Experimental[18]

Hydrazones Ia–i; XIIa,b (Table I).—A suspension of 0.1 mole of 3-carbethoxy-2-piperidone in 200 ml. of 0.5 *N* potassium hydroxide was stored at 30° for 18 hr. and filtered. The filtrate

(18) Melting points were determined on a Meliemp melting point aluminum block and are corrected. Infrared spectra were recorded on a Baird Model 455 spectrograph as Nujol mulls. Ultraviolet spectra were determined on a Beckman DK-2 spectrophotometer.

was treated with 10 ml. of 6 *N* hydrochloric acid and added with stirring at 0° to a fresh solution of substituted benzenediazonium chloride; the latter was prepared in the usual manner from 0.1 mole of substituted aniline in 191 ml. of 2.7 *N* hydrochloric acid and 0.102 mole of sodium nitrite in 25 ml. of water. The reaction mixture was adjusted to pH 3.5 by the addition of a solution of 25 g. of sodium acetate in 50 ml. water followed by stirring at 0–10° for 5 hr., yielding a precipitate. This was filtered, washed with cold water, and recrystallized either from 70% or 95% ethanol.

1,2,3,4-Tetrahydro-1-oxo-β-carbolines (IIa–d; Va,b; VIa,b) (Table II).—A solution of 0.1 mole of phenylhydrazone (Ia–d,f,g) in 100 ml. of 88% formic acid was refluxed for 4 hr. The reaction mixture was evaporated *in vacuo* to 0.25 vol. and diluted with several volumes of water. The precipitated product was filtered, washed with water, and recrystallized from formic acid or ethanol.

6-Isonicotinoyl-1,2,3,4-tetrahydro-1-oxo-β-carboline (IIe) (Table II).—A slurry of 10 g. of (*p*-isonicotinoylphenyl)hydrazone of 2,3-piperidinedione (Ie) in 150 g. of polyphosphoric acid was heated at 90° with stirring for 4 hr. The resulting thick sirup was then poured into ice–water and the precipitated yellowish product was collected on a filter. This was washed with cold water and purified by trituration with several 250-ml. portions of boiling 70% ethanol. The analytical sample was obtained by recrystallization from 30% formic acid.

2-Carboxytryptamines (IIIa–e; VIIa,b; IXa,b) (Table III).—A suspension of 1 g. of 1,2,3,4-tetrahydro-1-oxo-β-carboline (IIa–e; Va,b; VIa,b) in a solution of 2.5 g. of potassium hydroxide in 20 ml. of 60% ethanol was refluxed for 18 hr. After removal of ethanol *in vacuo*, the solution was treated with 12 ml. of water and adjusted to pH 6 with glacial acetic acid. The precipitated product was filtered, washed with cold water, and recrystallized from 50% ethanol.

Tryptamines (IVa–e; VIIIa,b) (Table IV).—A suspension of 1 g. of 2-carboxytryptamine (IIIa–e; VIIIa,b) in a solution prepared from 30 ml. of hydrochloric acid and 12 ml. of acetic acid was refluxed for a period of time which varied with the particular carboxytryptamine used. The refluxing times were 18 hr. for IIIb,c,e; 4 hr. for IIIa, VIIb; 3 hr. for VIIa; and 36 hr. for IIId. The reaction mixture was chilled and the precipitated hydrochloride of the unchanged starting material was removed by filtration. (This precipitate was observed only in course of the preparation of IIIa,b,c, and VIIa.) The filtrate was basified, to pH 11 while cooling by the addition of 40% potassium hydroxide, and extracted with eight 25-ml. portions of chloroform. Evaporating the dried chloroform solution gave a residue which was either recrystallized from water or converted to the hydrochloride by redissolving in ethanol and adding ethanolic hydrogen chloride. Purification of the salt was achieved by recrystallization from either absolute or 95% ethanol, with the exception of IVc which was recrystallized from 2-propanol–methanol (9:1).

Azepino[5,4,3-*cd*]indoles (Xa,b) (Table V).—A suspension of 1 g. of 4-acyl-2-carboxytryptamine (IXa,b) in a solution prepared from 30 ml. of 20% hydrochloric acid and 12 ml. of acetic acid was refluxed for 6 hr. The reaction mixture was cooled and adjusted to pH 11 by addition of 40% potassium hydroxide. The precipitated product was filtered, washed with water, and recrystallized from 50% ethanol.

3-Methyl- (or phenyl-)-2-(1,2,5,6-tetrahydro-2-oxo-3-pyridyl)-2H-indazole (XIa,b; Table VI).—A solution of 20 g. of *o*-acylphenylhydrazone of 2,3-piperidinedione (Ih,i) in 200 ml. of glacial acetic acid was refluxed for 6 hr. The reaction mixture was chilled and adjusted to pH 8 with ammonia. The precipitated product was filtered, washed with cold water, and recrystallized from ethyl acetate.

3-Methyl- (or phenyl-) -2-(2-oxo-3-piperidyl)-2H-indazole (XIIIa,b; Table VI). A. Cyclization of Hydrazones XIIa,b.—A solution of 9 g. of hydrazone XIIa,b in 45 ml. of 88% formic acid was refluxed for 3 hr. Concentration of the reaction mixture to 0.25 of its original volume and dilution with 50 ml. of water caused precipitation of a gum. Trituration of this with water gave a crystalline product which was filtered, washed with water, and recrystallized from ethyl acetate.

B. Catalytic Reduction of Indazolyltetrahydropyridones XIa,b.—A solution of 2 mmoles of XIa,b in 60 ml. of ethanol containing 50 mg. of 10% palladium-on-charcoal was hydrogenated at room temperature and atmospheric pressure. After 2.1 mmoles of hydrogen were taken up, the reaction mixture was filtered, and the filtrate evaporated to dryness. The residue was recrystallized from ethyl acetate.

5-Amino-2-(3-methyl- (or phenyl-) -2H-indazole-2-yl)-2-pentenoic Acid (XVa,b; Table VI) and 5-Amino-2-(3-phenyl-2H-indazole-2-yl)-pentanoic Acid (XVI; Table VI). A. Alkaline Hydrolysis.—A suspension of 1 g. of XIa,b, or XIIIb in a solution prepared from 2.5 g. of potassium hydroxide, 8 ml. of water, and 12 ml. of ethanol was refluxed for 6 hr. The reaction mixture was concentrated *in vacuo* until most of the ethanol was removed. Dilution with 12 ml. of water followed by adjustment to pH 6 by addition of acetic acid to the chilled solution gave a precipitate. This was filtered, washed with cold water, recrystallized from 50% ethanol, and dried over sulfuric acid in a vacuum desiccator.

B. Acidic Hydrolysis.—A solution of 1 g. of XIa,b, or XIIIb in 25 ml. of 20% hydrochloric acid was refluxed for 2 hr. and the reaction mixture was evaporated to dryness *in vacuo*. The residue was either recrystallized from water or converted to the free base by dissolving in water and adjusting the solution with ammonia to pH 6. The precipitated base was filtered, washed with cold water, and recrystallized from 50% ethanol.

3-(*o*-Ethylphenylhydrazo)-2-piperidone (XVII).—A solution of 1 g. of XIa in 50 ml. of ethanol was hydrogenated at room temperature and atmospheric pressure in the presence of 100 mg. of 10% palladium-on-charcoal for 5 days at which time hydrogen uptake had ceased. Evaporation of the filtered reaction mixture produced a white crystalline solid which was recrystallized from ethanol, m.p. 210–214°; yield 90%; λ_{max}^{EtOH} 197 mμ (ε 13,050), 232 mμ (ε 6200).

Anal. Calcd. for $C_{13}H_{19}N_3O$: C, 66.92; H, 8.21 N, 18.01. Found: C, 67.14; H, 8.40; N, 18.16.

3-(*o*-Ethylphenylhydrazo)piperidine (XVIII).—A solution of 1 g. of XVII in 50 ml. of tetrahydrofuran was reduced with 1 g. of lithium aluminum hydride at reflux temperature for 8 hr. Excess reagent was decomposed by dropwise addition of water, the reaction mixture was filtered, and the residue extracted several times with hot tetrahydrofuran. The filtrate and the extracts were combined, dried over sodium sulfate, and evaporated to dryness *in vacuo* to give an oily residue. This was dissolved in ether and the solution was treated with ethereal hydrogen chloride. The precipitated hydrochloride was purified by threefold recrystallization from 2-propanol acetone, m.p. 242–247°; yield 25%; λ_{max}^{EtOH} 230 mμ (ε 6400).

Anal. Calcd. for $C_{13}H_{21}N_3 \cdot 2HCl$: C, 53.42; H, 7.93; N, 14.38; Cl, 24.27. Found: C, 53.44; H, 8.21; N, 14.13; Cl, 24.05.

Reduction of 3-Phenyl-2-(1,2,5,6-tetrahydro-2-oxo-3-pyridyl)-2H-indazole (XIb) with Zinc and Acid.—A solution of 1 g. of XIb in a mixture of 10 ml. of concentrated hydrochloric acid and 100 ml. of acetic acid was heated on a steam bath and treated portionwise with 5 g. of zinc dust over a period of 4 hr. The solution was decanted from unchanged zinc, made alkaline with 40% potassium hydroxide, and extracted with chloroform. Combined extracts were dried over sodium sulfate and evaporated to dryness. The oily residue was purified by a passage in ethyl acetate through a 20-g. Florosil column and recrystallization of the crystalline fractions from ether. The product was identical with *o*-benzoylacetanilide, prepared according to ref. 16b.

Acknowledgment.—We are indebted to Drs. M. Ben, G. C. Boxill, J. F. Emele, J. Gylys, M. Osborne, R. J. Girerd, and B. Steinetz for biological studies. We wish to thank Miss B. Owendoff and Mr. R. Puchalski for spectral data and Mrs. U. Zeek and Mr. T. Wildeman for analytical determinations.