temperature for 5 min. Evolution of a colorless gas was observed. The reaction mixture was diluted with 10 ml of methanol, and the yellowish, crystalline precipitate was collected and washed with ether. Thus, 1.6 g of a mixture of starting material and 11 was obtained. Recrystallization from DMF–diethyl ether yielded 0.95 g (36%) of 11, mp 237°, identical in ir comparison with material obtained above. Dilution of the methanol filtrate with diethyl ether gave 0.6 g (32%) of 10, mp >300°, identical in ir comparison with material obtained above.

Registry No.—1, 872-50-4; 2, 7544-93-6; 4, 40387-20-0; 7, 40387-21-1; 10, 40387-22-2; 11, 40387-23-3; 12, 40387-24-4; 13, 40387-25-5; phenyl isocyanate, 103-71-9.

Quinazolines. I. The Oxidation of Indole-1,2-dicarboximides and Subsequent Conversion of Their Oxidation Products to Quinazolinones

KIKUO ISHIZUMI,* SHIGEHO INABA, AND HISAO YAMAMOTO

Pharmaceuticals Division, Sumitomo Chemical Company, Ltd., Takarazuka, Hyogo, Japan

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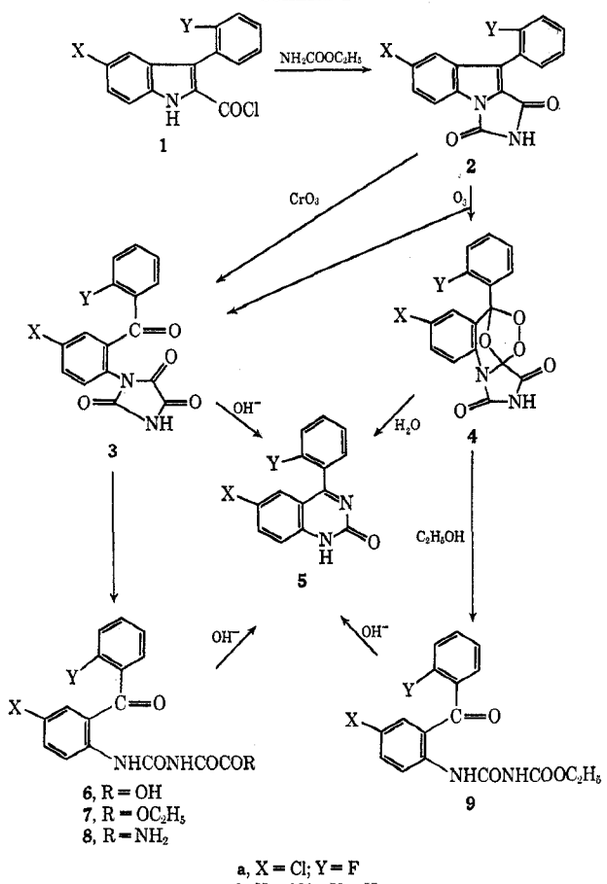
Chromic acid oxidation of indole-1,2-dicarboximides **2** led to imidazolidinetriones **3**, which on hydrolysis with base gave the corresponding dihydroquinazolinones **5**. Ozonolysis of **2**, on the other hand, resulted in the formation and isolation of crystalline ozonides **4**. On simply heating with water, the ozonides **4** were readily converted into **5** in nearly quantitative yields. The mechanism for this conversion is discussed.

In the past few years, we have reported the syntheses of 1,4-benzodiazepine ring systems by the oxidative ring cleavage of indoles bearing a substituent such as 2-aminomethyl,[1] 1-aminoethyl,[2] and 1-phthalimidoacetyl groups.[3] We have now extended our studies to another heterocyclic system, dihydroquinazolinone. Several reports have appeared in the literature on syntheses of the quinazoline ring system by rearrangement reactions of other heterocyclic structures, such as isatins,[4] quinolines,[5] and 1,4-benzodiazepines,[6] bearing an N-monosubstituted carbamoyl group at N-1. These methods, however, led only to the tetrahydroquinazolinones, rather than to the dihydro derivatives, because of the presence of a substituent on the carbamoyl nitrogen. We turned our attention to the synthesis and oxidation of indole-1,2-dicarboximides **2**. By analogy with the previously described conversion[2] of pyrazino[1,2-*a*]indol-1(2*H*)-ones into 2,3-dihydro-1*H*-1,4-benzodiazepines, compounds **2** seemed likely to produce the desired dihydroquinazolinones **5** by oxidative cleavage of the indole ring, followed by hydrolysis of the imidazolidinetriones **3** thus obtained (Scheme I).

The synthesis of **2** was achieved by condensation of indole-2-carboxylic acid chlorides[1c,d] with urethane.[7] The ir spectrum of **2** showed the expected NH absorptions and two carbonyl bands at relatively high frequencies (1790 and 1728 cm^{-1}), consistent with the hydantoin structure and in good agreement with those observed in the spectrum of *N*-phenylindole-1,2-dicarboximide.[8]

SCHEME I



Chromic Acid Oxidation.—When compounds **2** were treated with chromic acid in acetic acid at 60–70°, the expected imidazolidinetriones **3** were obtained together with small amounts of **5**. While **3a** was isolated only in amorphous form, **3b** formed a crystalline etherate, which on heating *in vacuo* was converted to free, crystalline **3b**. Their ir spectra showed carbonyl bands at 1750 cm^{-1} with a shoulder near 1790 cm^{-1}, owing to imidazolidinetrione structure,[9] as well as the benzophenone C=O absorption at 1670 cm^{-1}.

(1) (a) H. Yamamoto, S. Inaba, T. Hirohashi, and K. Ishizumi, *Chem. Ber.*, **101**, 4245 (1968); (b) S. Inaba, T. Hirohashi, and H. Yamamoto, *Chem. Pharm. Bull.*, **17**, 1263 (1969); (c) S. Inaba, K. Ishizumi, and H. Yamamoto, *ibid.*, **19**, 263 (1971); (d) S. Inaba, K. Ishizumi, K. Mori, and H. Yamamoto, *ibid.*, **19**, 722 (1971).

(2) S. Inaba, K. Ishizumi, T. Okamoto, and H. Yamamoto, *ibid.*, **20**, 1628 (1972).

(3) K. Ishizumi, K. Mori, S. Inaba, and H. Yamamoto, *ibid.*, **21**, 1027 (1973).

(4) (a) L. Capuano and M. Welter, *Chem. Ber.*, **101**, 3671 (1968); (b) L. Capuano, M. Welter, and R. Zander, *ibid.*, **103**, 2394 (1970).

(5) A. Brack, *Justus Liebigs Ann. Chem.*, **730**, 166 (1969).

(6) T. Masuda, S. Fujii, and K. Naito, Japanese Patent 15,500 (1971); *Chem. Abstr.*, **75**, 36104z (1971).

(7) The synthesis of indole-1,2-dicarboximide itself is achieved by condensing ethyl indole-2-carboxylate with the sodium derivative of urethane: J. D. Dutcher and A. Kjaer, *J. Amer. Chem. Soc.*, **73**, 4139 (1951).

(8) E. P. Papadopoulos and S. B. Bedrosian, *J. Org. Chem.*, **33**, 4551 (1968).

(9) H. Ulrich and A. A. R. Sayigh, *J. Org. Chem.*, **30**, 2781 (1965).

Hydrolysis of **3** with base gave the desired dihydroquinazolinones **5** in high yields. The structure of **5** was confirmed by comparison with authentic samples.[10] When **3a** was heated simply with water, the intermediate carbamoyloxamic acid **6a** was isolated, thus indicating that the imidazolidinetrione ring is initially opened at the anilino nitrogen. The position of the oxalyl group in **6a** was shown by the appearance of two exchangeable singlets at δ 10.95 and 11.15 in the nmr spectrum. Further hydrolysis of **6a** with base gave **5**. Ethanolysis or aminolysis of **3** also opened the imidazolidinetrione ring at the same position to give the oxamate **7** or oxamide **8**, respectively.

Ozonolysis.—Compound **2a** did not react with ozone in carbon tetrachloride, and only sluggishly in ethanol. However, when ozonized in acetic acid, **2a** went into solution and a new solid gradually precipitated in 43% yield, to which structure **4a** was assigned. The ir spectrum of **4a** exhibited carbonyl absorptions attributable to the hydantoin structure at somewhat higher frequencies than found with **2a** (1826 and 1742 cm^{-1}). The structure of **4a** was further supported by its ability to oxidize iodide ions. The acetic acid filtrates from the ozonolysis afforded a 40% yield of **3a**.

Ozonolysis of **2b** under similar conditions gave the soluble ozonide **4b**, which could be precipitated in 76% yield by addition of water to the ozonized solution.

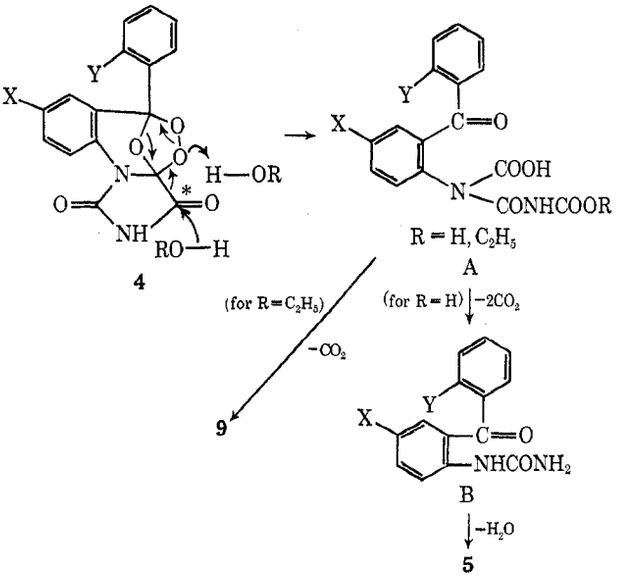
The use of acetic acid as a solvent for ozonolysis is known to be unfavorable for the formation of a stable ozonide because of its reactivity to a zwitterion intermediate.[11] However, we have shown previously[3] the formation of stable ozonides in acetic acid from some 3-phenyl-1-phthalimidoacetylindoles in which the indole 2,3 double bond is stabilized both by conjugation with the 3-phenyl group and by inhibition of the imino–ketimine tautomerism in the indole ring by an *N*-acyl group.[12] In view of the similarity of the double-bond system, therefore, the formation of **4** from acetic acid solvent was to be expected.[13]

Further conversion of ozonides **4** was best accomplished by hydrolysis, a method generally inferior to an oxidative or reductive work-up.[11] Hot water converted **4** to **5** in nearly quantitative yield with remarkable ease. A plausible mechanism is given in Scheme II in which the first step is nucleophilic attack by hydroxide at the starred carbonyl function.[15]

Subsequent loss of 2 mol of carbon dioxide followed by 1 mol of water from the allophanic acid intermediate A would give **5**. This mechanism is in good agreement with the observation that **4** was converted into ethyl allophanates **9** by the addition of ethanol.

Hydrolysis of **9** with base also gave **5** in high yields.

SCHEME II



Experimental Section

Infrared spectra were measured on a Hitachi Model EPI-G3 spectrophotometer and nmr spectra on a Varian T-60 instrument using tetramethylsilane as an internal standard. Mass spectra were taken on a Shimadzu LKB instrument with the direct sample inlet system and ionizing potential at 70 eV. All melting points were determined in open capillary tubes and are uncorrected.

5-Chloro-3-(*o*-fluorophenyl)indole-1,2-dicarboximide (2a). Method A.—A mixture of 30 g of 5-chloro-3-(*o*-fluorophenyl)-indole-2-carboxylic acid[1c] and 60 ml of thionyl chloride was heated under reflux for 2 hr. Excess of thionyl chloride was evaporated under reduced pressure. To the residual acid chloride (**1a**) was added 30 g of urethane. The mixture was heated to 170–180° for 2 hr. The resulting ethanol and excess reagent were distilled off under reduced pressure. The residue was triturated with ether and recrystallized from acetone to give 11.8 g of **2a**, mp 249–251.5°. A second crop (5.2 g, mp 248.5–251°) was obtained from the mother liquor to give a combined yield of 17.0 g (52.2%). Further recrystallizations from acetone gave yellow rods: mp 253–254°; ir (Nujol) 3130, 3025, 1790, 1728 cm^{-1}; mass spectrum *m/e* 314 (M^+), 271, 208.

Anal. Calcd for $C_{16}H_8ClFN_2O_2$: C, 61.07; H, 2.56; N, 8.90; Cl, 11.27. Found: C, 61.02; H, 2.66; N, 8.81; Cl, 11.13.

[4-Chloro-2-(*o*-fluorobenzoyl)phenyl]imidazolidinetrione (3a).—To a suspension of 2.0 g of **2a** in 30 ml of acetic acid was added a solution of 3 g of chromic anhydride in 3 ml of water. The mixture was stirred at 65° for 5 hr. Acetic acid was evaporated under reduced pressure. The residue was treated with water and extracted with ether, and the insoluble **5a** (0.05 g, 2.9%) was filtered off. The ether filtrate was dried over anhydrous sodium sulfate and evaporated. The residue was triturated with pentane and filtered to give 1.74 g (79.0%) of **3a** as an amorphous powder: ir (Nujol) 3230, 3075, 1792, 1755, 1673, 1613 cm^{-1}; nmr ($CDCl_3$) δ 6.95–7.70 (m, 7, aromatic H), 9.64 (s, 1, D_2O exchangeable, NH); mass spectrum *m/e* 346 (M^+), 275, 223, 180, 123 (*o*-FC_6H_4CO, base peak).

Anal. Calcd for $C_{16}H_8ClFN_2O_4$: C, 55.43; H, 2.33; N, 8.08; Cl, 10.23. Found: C, 54.90; H, 2.81; N, 7.98; Cl, 9.80.

(2-Benzoyl-4-nitrophenyl)imidazolidinetrione (3b).—A suspension of 5.0 g of **2b** was treated with a solution of 5 g of chromic anhydride in 5 ml of water in the same manner as above. After acetic acid was evaporated, the residue was triturated with water, and the solid, which was separated by filtration, was dried in a vacuum desiccator at room temperature. This gave 5.55 g of crude **3b**, mp 135–140°. The crude product was suspended in ether and heated under reflux. The insoluble solid was removed by filtration, and the filtrate was concentrated to a small volume and chilled in a refrigerator. The precipitate formed was collected by filtration to give 3.41 g (50.7%) of the etherate of **3b**

(10) S. Inaba, M. Yamamoto, K. Ishizumi, K. Takahashi, K. Mori, and H. Yamamoto, German Patent 1,935,404 (1970); *Chem. Abstr.*, **72**, 90494c (1970).

(11) P. S. Bailey, *Chem. Rev.*, **58**, 926 (1958).

(12) C. M. Atkinson, J. C. E. Simpson, and A. Taylor, *J. Chem. Soc.*, 165 (1954).

(13) Stable ozonides from acetic acid solvent have also been reported in 1,2-diphenylindene[14a] and 2-methyl-3-phenylindenone[14b] where the double bond is conjugated with the phenyl or carbonyl group.

(14) (a) P. S. Bailey, *Chem. Ber.*, **87**, 993 (1954); (b) R. Criegee, P. de Bruyn, and G. Lohaus, *Justus Liebigs Ann. Chem.*, **583**, 19 (1953).

(15) A similar mechanism has been proposed for "abnormal" ozonolyses of α,β-unsaturated acids, aldehydes, and ketones, assuming the formation of an ozonide: D. H. R. Barton and E. Seoane, *J. Chem. Soc.*, 4150 (1956). On the other hand, Bailey[11] has explained those ozonolyses by the zwitterion rearrangement mechanism.

as colorless prisms: mp 90–94° dec; ir (Nujol) 3550, 3300–2720, 1790, 1760, 1672, 1622, 1600 cm^{-1}; nmr ($CDCl_3$) δ 1.20 (t, 6, J = 7 Hz, 2 CH_3), 3.52 (q, 4, J = 7 Hz, 2 CH_2), 7.30–8.50 (m, 8, aromatic H).

Anal. Calcd for $C_{20}H_{19}N_3O_7$: C, 58.11; H, 4.63; N, 10.16. Found: C, 58.15; H, 4.52; N, 10.15.

The etherate, on heating at 70° in a vacuum oven, gave pure, ether-free **3b** as colorless prisms: mp 165–168° dec (softening at 117°); ir (Nujol) 3225, 3075, 1795, 1757, 1672, 1620, 1600 cm^{-1}.

Anal. Calcd for $C_{16}H_9N_3O_6$: C, 56.65; H, 2.67; N, 12.39. Found: C, 56.93; H, 2.55; N, 12.36.

Hydrolysis of 3a to 5a. Method B.—A mixture of 0.20 g of **3a**, 6 ml of ethanol, and 0.8 ml of 20% sodium hydroxide solution was refluxed for 45 min. After evaporation of ethanol, the residue was diluted with water and acidified with hydrochloric acid. The precipitate was collected by filtration, washed with water, and dried to give 0.14 g (88.4%) of **5a**, mp >300°. Recrystallization from dimethylformamide afforded yellow needles, mp >300°. The material was identical with an authentic sample[10] by comparison of ir spectra.

Anal. Calcd for $C_{14}H_8ClFN_2O$: C, 61.22; H, 2.94; N, 10.20; Cl, 12.91. Found: C, 61.29; H, 2.90; N, 10.12; Cl, 12.88.

[4-Chloro-2-(*o*-fluorobenzoyl)phenyl]carbamoyloxamic Acid (6a).—A suspension of 0.50 g of **3a** in 7 ml of water was heated in a water bath for 3.5 hr. After cooling, the precipitate was collected by filtration and washed with ether to give 0.45 g (85.6%) of **6a**, mp 199.5–200° dec. Recrystallization from ethylene dichloride afforded slightly yellow needles: mp 198° dec; ir (Nujol) 3160, 1714, 1653 cm^{-1}; nmr (DMSO) δ 7.20–8.30 (m, 7, aromatic H), 10.95 (s, 1, D_2O exchangeable, NH), 11.15 (s, 1, D_2O exchangeable, NH); mass spectrum m/e 346 ($M - H_2O$), 275, 180, 123 (o-FC_6H_4CO, base peak).

Anal. Calcd for $C_{16}H_{10}ClFN_2O_5$: C, 52.69; H, 2.76, N, 7.68. Found: C, 53.04; H, 3.04; N, 7.81.

Compound **6a** was hydrolyzed with sodium hydroxide solution as described in method B to give **5a** in 96.3% yield.

Ethyl [4-Chloro-2-(*o*-fluorobenzoyl)phenyl]carbamoyloxamate (7a). Method C.—A solution of 0.20 g of **3a** in 3 ml of ethanol was heated under reflux for 6.5 hr. The reaction mixture was cooled, and the precipitate that formed was collected by filtration to give 0.04 g of **7a**, mp 192–193° dec. On heating the filtrate, a further 0.08 g of product was obtained to give a combined yield of 0.12 g (53.0%). Recrystallization from ethanol afforded colorless needles: mp 199–200° dec; ir (Nujol) 3307, 3155, 1720, 1667, 1657, 1616 cm^{-1}.

Anal. Calcd for $C_{18}H_{14}ClFN_2O_5$: C, 55.04; H, 3.59; N, 7.13; Cl, 9.03. Found: C, 55.01; H, 3.71; N, 7.15; Cl, 9.08.

[4-Chloro-2-(*o*-fluorobenzoyl)phenyl]carbamoyloxamide (8a).—A suspension of 0.20 g of **3a** in 2 ml of concentrated ammonium hydroxide was stirred at room temperature for 3 hr. Filtration and washing with water gave 0.19 g (90.6%) of **8a**, mp 207–208° dec. After recrystallization from a mixture of dimethylformamide and ethanol, slightly yellow needles were obtained: mp 212–212.5° dec; nmr (DMSO) δ 7.30–8.52 (m, 7, aromatic H), 8.28 and 8.35 (2, D_2O exchangeable, $CONH_2$), 10.40 (s, 1, D_2O exchangeable, NH), 11.53 (s, 1, D_2O exchangeable, NH).

Anal. Calcd for $C_{16}H_{11}ClFN_3O_4$: C, 52.83; H, 3.05; N, 11.55; Cl, 9.75. Found: C, 52.77; H, 3.07; N, 11.56; Cl, 9.78.

5-Chloro-3-(*o*-fluorophenyl)indole-1,2-dicarboximide Ozonide (4a).—An ozone–oxygen stream[16] was passed through a stirred suspension of 1.0 g of **2a** in 25 ml of acetic acid for 3 hr. During the course of the reaction, **2a** went into solution and then a new fine white suspension appeared. The white precipitate was collected by filtration, washed with water, and dried in a vacuum desiccator to give 0.41 g of **4a**, mp 136.5–137° dec. The filtrate was concentrated to a small volume to give an additional 0.09 g of **4a** for a combined yield of 0.50 g (43.4%): ir (Nujol) 3190, 3075, 1826, 1741, 1621 cm^{-1}; mass spectrum m/e 275, 180.

(16) Ozone was generated from oxygen using a Nippon ozone 0-10-2 ozonator.

The ozonide **4a** gave a positive active oxygen test with sodium iodide in acetic acid solution.

Anal. Calcd for $C_{16}H_8ClFN_2O_5$: C, 52.98; H, 2.22; N, 7.72; Cl, 9.77. Found: C, 52.64; H, 2.40; N, 7.62; Cl, 9.78.

The filtrate from which the second crop was filtered was evaporated to dryness under reduced pressure below 40°. The residue was dissolved in ether, washed with water, and dried over anhydrous sodium sulfate. Evaporation of the solvent and trituration with pentane gave 0.44 g (39.9%) of **3a**. The ir and nmr spectra of this compound were identical with those of the product obtained above from chromic acid oxidation of **2a**.

5-Nitro-3-phenylindole-1,2-dicarboximide Ozonide (4b).—A suspension of 5.0 g of **2b** in 125 ml of acetic acid was ozonized as above. The resulting solution was diluted with cold water. The precipitate that formed was collected by filtration, washed with water, and dried to give 4.4 g (76.1%) of **4b**: mp 100° dec; ir (Nujol) 3600, 3500, 3225, 1828, 1809, 1775, 1620, 1598 cm^{-1}. This material also gave a positive active oxygen test.

Anal. Calcd for $C_{16}H_9N_3O_7$: C, 54.09; H, 2.55; N, 11.83. Found: C, 54.29; H, 2.57; N, 11.85.

Conversion of 4a to 5a. Method D.—A suspension of 0.10 g of **4a** in 3 ml of water was heated to 70–80° for 1 hr. Cooling and filtration gave 0.07 g (92.4%) of **5a**, mp > 300°. The ir spectrum of this compound was identical with that of the sample obtained by hydrolysis of **3a**.

Ethyl 4-[4-Chloro-2-(*o*-fluorobenzoyl)phenyl]allophanate (9a). Method E.—To 2 ml of ethanol was added 0.10 g of **4a**. Evolution of carbon dioxide immediately occurred. The mixture was refluxed for 1 hr and cooled. The precipitate was collected by filtration to give 0.09 g (89.5%) of **9a**, mp 208–209° dec. Recrystallization from ethanol afforded colorless needles: mp 208–209° dec; ir (Nujol) 3130, 1740, 1715, 1665, 1618 cm^{-1}; nmr (DMSO) δ 1.24 (t, 3, J = 7 Hz, CH_3), 4.20 (q, 2, J = 7 Hz, CH_2), 7.20–8.40 (m, 7, aromatic H), 10.48 (s, 1, D_2O exchangeable, NH), 11.45 (s, 1, D_2O exchangeable, NH); mass spectrum m/e 364 (M^+), 275, 180, 123 (o-FC_6H_4CO, base peak).

Anal. Calcd for $C_{17}H_{14}ClFN_2O_4$: C, 55.98; H, 3.87; N, 7.68; Cl, 9.72. Found: C, 56.29; H, 3.85; N, 7.47; Cl, 9.64.

Compound **9a** was hydrolyzed with sodium hydroxide solution as in method B to give **5a** in 93.6% yield.

The remaining **b** compounds were prepared as described for **a** series and are given in Table I.

TABLE I

COMPOUNDS **2b**, **5b**, **7b**, AND **9b**[a]

Compd	Method	Recrystn solvent	Mp, °C	Yield, %
2b	A	Acetone	262–262.5	50.2
5b[b]	B	EtOH	>300	87.9
5b[b]	D	EtOH	>300	92.0
7b	C	EtOH	213–214	59.0
9b	E	EtOH	202–203	80.1[c]

[a] Satisfactory analytical data (±0.3% for C, H, and N) were reported for all new compounds listed in the table: Ed. [b] The ir spectrum of this material was identical with that of an authentic sample.[10] [c] This reaction yielded **5b** in 12.5% yield as a by-product isolated from the reaction filtrate.

Registry No.—**1a**, 32502-22-0; **1b**, 30016-54-7; **2a**, 40387-03-9; **2b**, 40387-04-0; **3a**, 40387-05-1; **3b**, 40387-06-2; **3b** etherate, 40387-07-3; **4a**, 40387-08-4; **4b**, 40387-09-5; **5a**, 40069-75-8; **5b**, 26313-36-0; **6a**, 40387-12-0; **7a**, 40387-13-1; **7b**, 40387-14-2; **8a**, 40387-15-3; **9a**, 40387-16-4; **9b**, 40387-17-5; 5-chloro-3-(*o*-fluorophenyl)indole-2-carboxylic acid, 40387-18-6; thionyl chloride, 7719-09-7.