absorption of oxygen and whether it was reversible as in the oxygen-carrying chelates described by Calvin, Bailes and Wilmarth[6] the following experiment was performed: A Pyrex sample tube with an outside diameter small enough to fit inside a closable absorption tube used for carbon and hydrogen determinations was constructed at one end, and plugged with glass wool at both ends. It was placed inside a test-tube and dried to constant weight in a vacuum at 100°. The weighings were taken with the tube filled with nitrogen. About 20 mg. of imidazole–ferroprotoporphyrin, which had been dried in a vacuum at 100° for six hours, was quickly placed in the sample tube, and this in turn inserted in the absorption tube, which had been previously weighed. Nitrogen was passed through the absorption tube and it was again weighed. A blank determination was run by transferring the sample tube to the drying apparatus and, after drying it for half an hour, replacing it in the absorption tube, passing nitrogen through the assembly, and then weighing it. This weight, within the limits of experimental error, was identical to the preceding one. From this weight and that of the sample tube, the weight of the sample was calculated. Then dry air was passed through the assembly at the rate of 20 cc. per minute for eight hours and, after sweeping it with nitrogen for 15 minutes, its weight was determined; weight of sample, 10.234 mg.; weight after passing in air, 10.644 mg.; increase, 4.01%, calculated on the basis of one mole of oxygen to one mole of imidazole complex, 4.25%. Hence, 0.94 mole of oxygen was absorbed. The sample was then heated for four hours at 100° in a vacuum and weighed again: weight after regeneration, 10.240 mg. In another experiment the increase in weight was 4.12% corresponding to 0.97 mole of oxygen per mole of complex. This sample was deoxygenated by placing it inside of a water condenser heated with steam through which a current of pure nitrogen was passed for six hours. Upon submitting it to a current of air again, it absorbed 3.8% of its original weight of oxygen.

(6) M. Calvin, R. H. Bailes and W. K. Wilmarth, THIS JOURNAL, **68**, 2254 (1946).

Purification of Solvents.—Diethyl ether was dried over calcium chloride and distilled over sodium through a long column in an all-glass apparatus, discarding first and last runnings. It was stored over sodium wire and distilled before use. Methyl alcohol was refluxed four hours over powdered CaO, distilled twice in a nitrogen atmosphere from an all-glass still and stored in a flask maintained at constant nitrogen pressure. Pyridine was dehydrated for ten days over BaO, distilled over BaO in a nitrogen atmosphere, and redistilled. The water and glacial acetic acid used in the preparation of heme were distilled twice in a nitrogen atmosphere and stored in flasks maintained at constant nitrogen pressure.

BALTIMORE 18, MD.

[CONTRIBUTION FROM ABBOTT LABORATORIES]

The Reactions of Dibromoalkanes and *o*-(Bromoalkyl)-α-bromotoluenes with *o*-Substituted Anilines. The Synthesis of 1-Arylpyrrolidines and Related Compounds

BY ARMIGER H. SOMMERS

RECEIVED DECEMBER 7, 1955

The reaction of 1,4-dibromoalkanes with *o*-substituted and *o,o'*-disubstituted anilines yielded only 1-arylpyrrolidines except in one case when a low yield of the substituted 1,4-diaminoalkane was obtained. Similarly, 2-(β-bromoethyl)-α-bromotoluene gave only 2-aryl-1,2,3,4-tetrahydroisoquinolines, while α,α'-dibromo-*o*-xylene gave principally 2-arylisoindolines together with small amounts of substituted α,α'-diamino-*o*-xylenes. 1,3-Dibromopropane and 1,6-dibromohexane yielded no cyclic products from this reaction, even when *ortho* groups were not present in the amine. The reactions of phthalic and homophthalic anhydrides with substituted anilines were also investigated as a route toward alternate syntheses of some of these cyclic amines, and a novel by-product from lithium aluminum hydride reduction of a substituted phthalimide was observed.

The reaction of 1,5-dibromopentane upon *o*-substituted aromatic amines recently was shown to give principally the corresponding 1-arylpiperidines[1] rather than the 1,5-diarylaminopentanes which had been described earlier as the only products.[2] Three of these hindered amines have now been treated with other dibromoalkanes and with two aralkylene dibromides to observe the extent of formation of four-, five- or seven-membered rings.

1,3-Dibromopropane and 1,6-dibromohexane reacted with *o*-toluidine, and with aniline as well, to give only open chain diamines. Although Scholtz reported the formation of a low yield of 1-phenylazetidine[3] from 1,3-dibromopropane and aniline, Veer in more recent work failed to obtain the cyclic product.[4] Von Braun observed similar results using 1,6-diiodohexane and aniline.[5] Aliphatic[6] and aromatic[7] primary amines are known to yield 1-substituted pyrrolidines when treated with 1,4-dibromo- or 1,4-dichlorobutane. The ease of pyrrolidine ring formation from 1,4-dibromobutane seems greater than that of piperidine ring formation from 1,5-dibromopentane, for the latter gives only the open-chain diamine I on reaction with 2,6-dimethylaniline,[1] while 1,4-dibromobutane has now been found to yield 1-(2,6-dimethylphenyl)-pyrrolidine (II) with no evidence of diamine formation. 1-Arylpyrrolidines were also formed as the only products when *o*-toluidine, *o*-anisidine and *m*-anisidine reacted with 1,4-dibromobutane. In the last case, where there is no *ortho* substituent, the yield was significantly higher. Several derivatives of the methoxyphenylpyrrolidines were prepared, including the corresponding phenols.

In their study of the influence of *o*-substitution on the reaction of anilines with 1,4-dibromopentane in solvents, Scholtz and Friemehlt report that *o*-toluidine gives only N,N'-di-(*o*-tolyl)-1,4-diaminopentane[8] (IVa) and conclude that the presence

(1) A. H. Sommers and S. E. Aaland, THIS JOURNAL, **75**, 5280 (1953).

(2) M. Scholtz and E. Wassermann, *Ber.*, **40**, 852 (1907).

(3) M. Scholtz, *ibid.*, **32**, 2251 (1899).

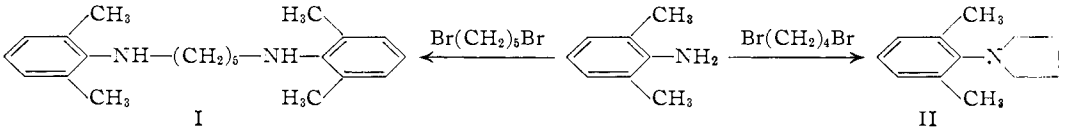
(4) W. L. C. Veer, *Rec. trav. chim.*, **57**, 989 (1938).

(5) J. von Braun, *Ber.*, **43**, 2853 (1910).

(6) R. C. Elderfield and H. A. Hageman, *J. Org. Chem.*, **14**, 605 (1949); D. D. Libman, D. L. Pain and R. Slack, *J. Chem. Soc.*, 2305 (1952); J. G. Erickson and J. S. Keps, THIS JOURNAL, **77**, 485 (1955).

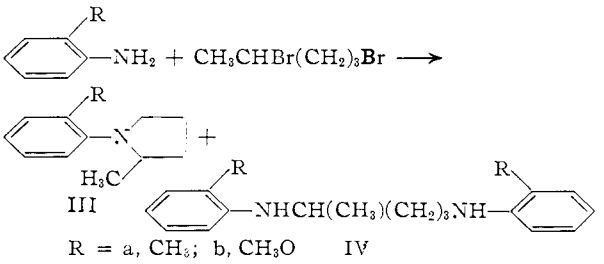
(7) L. C. Craig with R. M. Hixon, *ibid.*, **52**, 804 (1930); O. Wichterle and M. Vavruska, *Chem. Listy*, **46**, 237 (1952); *C. A.* **47**, 4330 (1953).

(8) M. Scholtz and P. Friemehlt, *Ber.*, **32**, 848 (1899).



I II

of *ortho* groups generally prevents the ring closure of 1,4-dibromides on aromatic amines. Elderfield and Green showed, however, that treatment of 6-methoxy-8-aminoquinoline with 1,4-dibromopentane gave 6-methoxy-8-(2-methylpyrrolidinyl)-quinoline[9] rather than the substituted 1,4-diaminopentane which would be expected if this were true. We isolated only a very small amount of the diamine IVa from the reaction of this dibromide with *o*-toluidine and found that the major product is 1-(*o*-tolyl)-2-methylpyrrolidine (IIIa). Normant has shown that small amounts of linear diamines analogous to IV may be formed from 1,4-dibromoalkanes and aniline,[10] which contains no hindering group.

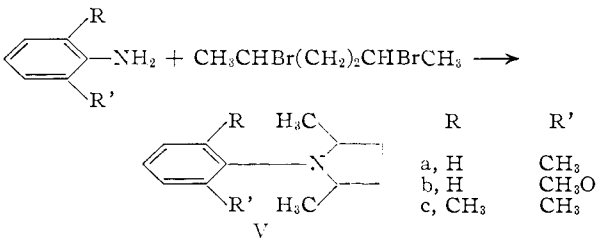


III IV

R = a, CH_3; b, CH_3O

The reaction of *o*-anisidine with 1,4-dibromopentane gave us only the cyclic compound, 1-(2-methoxyphenyl)-2-methylpyrrolidine (IIIb).

A third dibromide, 2,5-dibromohexane, which contains two secondary alkyl bromide groups, gave comparable yields of substituted pyrrolidines V in these reactions. None of the possible diamines was



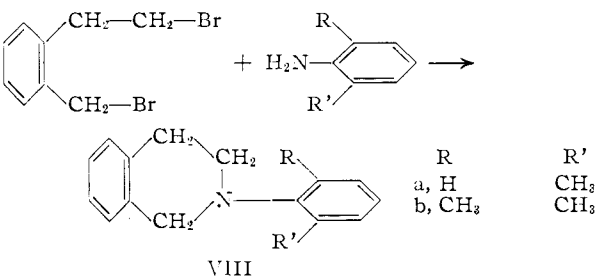
R	R'
a, H	CH_3
b, H	CH_3O
c, CH_3	CH_3

V

isolated. The various 1-arylpyrrolidines and their derivatives are summarized in Table I.

acterization of ring-substituted anilines.[12] We have found, however, that this reaction gives both the isoindoline and the diamine, with the former as the major product. This is true even when both *ortho* positions are substituted, as in 2,6-dimethylaniline. Because of the suggestion by Roberts and Ross that the presence of a solvent may affect the course of a reaction of this sort,[13] the conditions of Scholtz were duplicated with results essentially the same as those observed without solvent. Only 2-phenylisoindoline was obtained when aniline was used and no hindering *ortho* groups were present.

A comparison of the ease of formation of 2-aryltetrahydroisoquinolines with that of the isoindolines described above was made by using 2-(β-bromoethyl)-α-bromotoluene, which is reported to undergo ready ring closure with primary amines.[14] We found that it reacts with *o*-toluidine and with 2,6-dimethylaniline to give only the corresponding 2-aryltetrahydroisoquinolines (VIII). This is in contrast to the reaction of α,α′-dibromo-*o*-xylene, which resulted in formation of the diamines as well as the cyclic products.

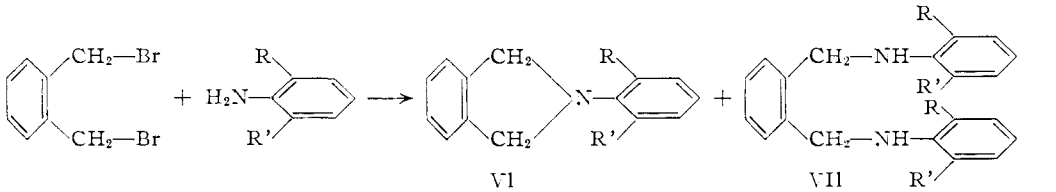


R	R'
a, H	CH_3
b, CH_3	CH_3

VIII

It therefore seems evident that six members are preferred in ring formation by the reaction of *o*-(bromoalkyl)-α-bromotoluenes with hindered anilines, while five-membered ring formation is favored with dibromoalkanes. Recent work indicates that the latter conclusion is true also when hydrazine is used.[15]

Recent reports describing the preparation of substituted isoindolines by reduction of phthalimides



VI VII

R = a, CH_3; b, CH_3O; c, CH_3. R′ = a, H; b, H; c, CH_3.

The repeated statement[11] that α,α′-dibromo-*o*-xylene acts selectively on *o*-substituted aromatic amines to yield diamines VII rather than isoindolines VI has led to a proposed method for the char-

(9) R. C. Elderfield and M. Green, *J. Org. Chem.*, **17**, 431 (1952).

(10) H. Normant, *Compt. rend.*, **226**, 1734 (1948).

(11) M. Scholtz, *Ber.*, **31**, 414, 627, 1154, 1707 (1898); M. Scholtz and R. Wolfrum, *ibid.*, **43**, 2304 (1910).

(12) J. Houben, "Die Methoden der Organischen Chemie," Third Edition, Vol. 4, Georg Thieme, Leipzig, 1941, (Edwards Brothers, Inc., Ann Arbor, Michigan, 1944), p. 581; R. C. Elderfield, "Heterocyclic Compounds," Vol. 3, John Wiley and Sons, Inc., New York, N. Y., 1952, p. 281.

(13) J. J. Roberts and W. C. J. Ross, *J. Chem. Soc.*, 4288 (1952).

(14) J. von Braun and F. Zobel, *Ber.*, **56**, 2142 (1923); F. G. Holliman and F. G. Mann, *J. Chem. Soc.*, 34 (1945).

(15) C. G. Overberger, L. C. Palmer, B. S. Marks and N. R. Byrd, THIS JOURNAL, **77**, 4100 (1955).

TABLE I: 1-ARYLPYRROLIDINES AND SALTS

R_1	R_2	R_3	R_4	Yield, %	B.p. °C.	Mm.	$n^{25}D$	Formula	Carbon, % Calcd.	Found	Hydrogen, % Calcd.	Found	Nitrogen, % Calcd.	Found	Picrates M.p., °C.	Nitrogen, % Calcd.	Found	Hydrochlorides M.p., °C.	Nitrogen, % Calcd.	Found
H[a]	H	H	H	75	174	20	1.5767	$C_{11}H_{15}NO$	74.54	74.74	8.53	8.76	7.90	7.98	156–157	13.79	13.78	158–160	6.56	6.63
H[b]	H	H	H	92	133–134[c]			$C_{10}H_{13}NO$	73.59	73.78	8.03	7.86	8.58	8.62				137–138	7.02	7.13
CH_3[d]	H	H	H	35	114	11	1.5593	$C_{11}H_{15}N$	81.94	81.78	9.38	9.38	8.69	8.85	140–142	14.35	14.68	132–134	7.09	7.11
CH_3O	H	H	H	44	139	10	1.5694	$C_{11}H_{15}NO$	74.54	74.74	8.53	8.56	7.90	8.00	153–154	13.79	13.91	129–130	6.56	6.49
HO	H	H	H	95	108–109[e]			$C_{10}H_{13}NO$	73.59	73.47	8.03	7.94	8.58	8.68				170–171[e]	5.74	5.84
[f]	H	H	H	57	131	0.1	1.5637	$C_{13}H_{18}N_2O_2$	66.64	66.54	7.74	7.56	11.96	11.98	[g]			150–152	10.35	10.55
CH_3	CH_3	H	H	31	110	9	1.5328	$C_{12}H_{17}N$	82.23	82.33	9.78	9.89	7.99	8.10	154–155	13.86	13.86	148–151	6.62	6.62
CH_3[h]	H	CH_3	H	28	116–117	16	1.5376	$C_{12}H_{17}N$	82.23	82.16	9.78	9.47	7.99	8.20	119–120	13.86	13.96			
CH_3O	H	CH_3	H	33	137–138	15	1.5542	$C_{12}H_{17}NO$	75.35	75.70	8.96	8.63	7.32	7.23	167	13.33	13.31			
HO	H	CH_3	H	79	67–68	0.1	1.5418	$C_{11}H_{15}NO$	74.54	74.65	8.53	8.71	7.90	8.07	148–151	13.79	13.65			
CH_3	H	CH_3	CH_3	28	119–121	20	[i]	$C_{13}H_{19}N$	82.48	83.12	10.12	10.38	7.40	7.31	164–166	[j]		157–173	6.21	6.19
CH_3O	H	CH_3	CH_3	30	136–138	20	1.5340	$C_{13}H_{19}NO$	76.05	76.16	9.33	9.43	6.82	7.02	133–135	12.90	12.95	156–158	5.79	5.93
HO	H	CH_3	CH_3	40	57	0.1	1.5271	$C_{12}H_{17}NO$	75.35	75.10	8.96	8.94	7.32	7.30	158–163	13.33	13.53	235–247	6.15	6.31
CH_3	CH_3	CH_3	CH_3	12	127–128	17	1.5290	$C_{14}H_{21}N$	82.70	82.66	10.41	10.13	6.89	7.28	139–140	12.96	13.09			

[a] 1-(*m*-Methoxyphenyl)-pyrrolidine. [b] 1-(*m*-Hydroxyphenyl)-pyrrolidine. The *methiodide* salt, recrystallized in acetone, melted at 142°. *Anal.* Calcd. for $C_{11}H_{16}INO$: C, 43.29; H, 5.29. Found: C, 43.57; H, 5.12. [c] Melting point. [d] Yu. K. Yur'ev and G. A. Minkina, *J. Gen. Chem.* (*U.S.S.R.*), **7**, 2945 (1937); *C. A.*, **32**, 5399 (1938), have described this base obtained from tetrahydrofuran and give m.p. 102° for the picrate. The higher refractive index of their product, $n^{20}D$ 1.5658, indicates the possibility of some *o*-toluidine remaining as an impurity. [e] Hydrobromide. [f] $(CH_3)_2NCOO$. [g] Two forms isolated. See Experimental. [h] Yu. K. Yur'ev, V. A. Tronova, N. A. L'vova and Z. Ya. Bukshpan, *J. Gen. Chem.* (*U.S.S.R.*), **11**, 1128 (1941); *C. A.*, **37**, 4071 (1943), have prepared this base in low yield from 2-methyltetrahydrofuran and *o*-toluidine. [i] $n^{25}D$ 1.5169–1.5209. [j] Calcd.: C, 54.54; H, 5.30. Found: C, 54.92; H, 5.53.

with lithium aluminum hydride[16] suggested independent syntheses of some of the above isoindolines and tetrahydroisoquinolines. The reaction of phthalic anhydride with 2,6-dimethylaniline without solvent gave 2-(2,6-dimethylphenyl)-phthalimide (IX)[17]; when run in acetic acid[18] it gave N-(2,6-dimethylphenyl)-phthalamic acid (XI). Reduction with lithium aluminum hydride of the substituted phthalimide IX gave the expected 2-(2,6-dimethylphenyl)-isoindoline (VIc), as well as a neutral by-product, proved to be N-(2,6-dimethylphenyl)-2-hydroxymethylbenzamide (X). Other

reports describe a lactam,[19] an olefinic lactam[20] and a hydroxy lactam[21] which were obtained by treatment of various imides with lithium aluminum hydride. Although a saturated amine is the usual product, lactams also may give rise under these conditions to unsaturated nitrogen heterocycles[22] or, when elimination of hydrogen from the α-position is not feasible, to aminocarbinols, sometimes with ring opening.[23] The formation of X may be analogous to the last case and is compatible with the mechanism proposed by Gaylord which postulates the presence of a free carbonyl group during the reduction of an amide by lithium aluminum hydride.[24] The structure of X was established by an alternate synthesis from XI, and by further reduction to the aminocarbinol XII.

(16) M. Spillmann and K. Hoffmann, *Helv. Chim. Acta*, **37**, 1699 (1954); D. E. Sunko and M. Prostenick, *Arhiv Kem.*, **26**, 7 (1954); L. M. Rice, C. H. Grogan and E. E. Reid, THIS JOURNAL, **77**, 616 (1955).

(17) G. Vanags, *Acta Univ. Latviensis, Kim. Fakultat*, Ser. 4, No. 8, 405 (1939); *C. A.*, **34**, 1982 (1940).

(18) G. Wanag and A. Veinbergs, *Ber.*, **75B**, 736 (1942).

(19) J. O. Halford and B. Weissmann, *J. Org. Chem.*, **17**, 1646 (1952).

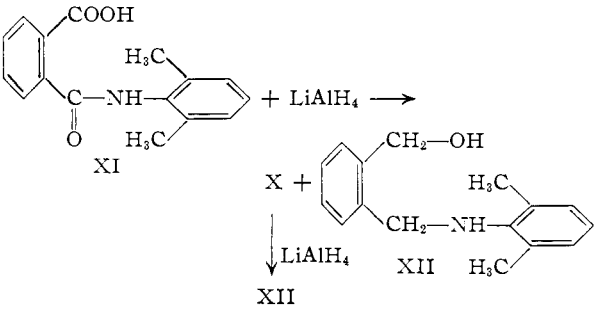
(20) R. Lukes and M. Ferles, *Coll. Czech. Chem. Comm.*, **18**, 818 (1953).

(21) E. Tagmann, E. Sury and K. Hoffmann, *Helv. Chim. Acta*, **37**, 185 (1954).

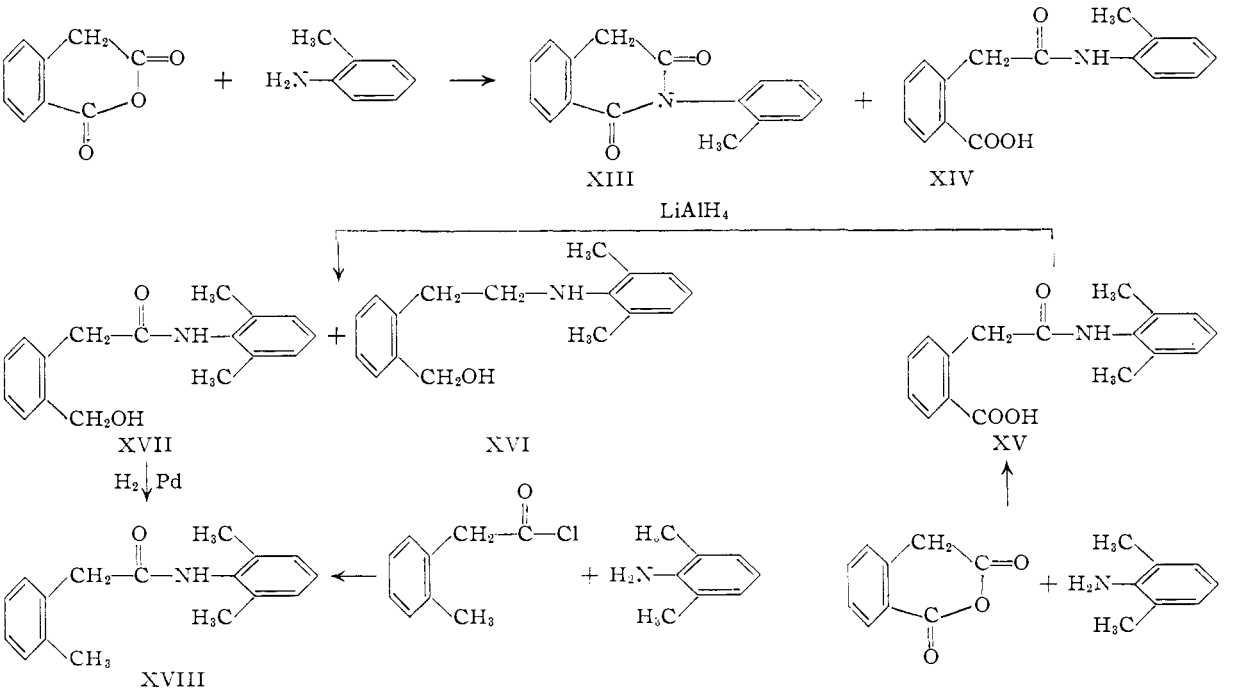
(22) P. L. Julian and H. C. Printy, THIS JOURNAL, **71**, 3206 (1949); S. P. Findlay, *ibid.*, **73**, 3008 (1951); J. W. Cook, J. D. Loudon and P. McCloskey, *J. Chem. Soc.*, 3904 (1952); G. Wittig, G. Closs and F. Mindermann, *Ann.*, **594**, 89 (1955).

(23) M. E. Speeter and W. H. Maroney, THIS JOURNAL, **76**, 5810 (1954). See also the references given by these authors.

(24) N. G. Gaylord, *Experientia*, **10**, 423 (1954).



By heating homophthalic anhydride with 2,6-dimethylaniline we obtained only N-(2,6-dimethylphenyl)-2-carboxyphenylacetamide (XV). When *o*-toluidine was used, very low yields of the corresponding amide XIV and of 2-(*o*-tolyl)-1,2,3,4-tetrahydroisoquinoline-1,3-dione (XIII) were isolated. Therefore no 2-aryltetrahydroisoquinolines VIII were prepared by the reduction of cyclic imides. As had been the case with its homolog XI, the carboxyphenylacetamide XV yielded a mixture of amide–alcohol XVII and amine–alcohol XVI when treated with lithium aluminum hydride. Catalytic hydrogenation of N-(2,6-dimethylphenyl)-2-hydroxymethylphenylacetamide (XVII) afforded N-(2,6-dimethylphenyl)-*o*-tolylacetamide (XVIII), identical with authentic material prepared from *o*-tolylacetyl chloride. The course of ring opening of homophthalic anhydride by aromatic amines was thereby established.



Experimental

Reaction of Dibromoalkanes with Aromatic Amines

A. 1,3-Dibromopropane. With *o*-Toluidine.—A mixture of five moles of *o*-toluidine and one mole of 1,3-dibromopropane was heated on the steam-bath for one hour during which time a crystalline solid formed. This was stirred with dry ether and filtered to give two moles of *o*-toluidine hydrobromide. The filtrate was distilled, and 0.63 mole of **N,N'-di-(*o*-tolyl)-1,3-propanediamine**, b.p. 151–152° at 0.1 mm., $n^{25}D$ 1.6009, was obtained as a light yellow oil which crystallized on standing, and melted at 40–44°.

Anal. Calcd. for $C_{17}H_{22}N_2$: N, 11.02. Found: N, 11.15.

The dihydrochloride salt crystallized from absolute ethanol and melted at 214–216°.

Anal. Calcd. for $C_{17}H_{24}Cl_2N_2$: N, 8.56. Found: N, 8.36.

Scholtz prepared the diamine in the same manner except that the reaction was carried out in alcohol.[3]

With Aniline.—A 65% yield of **N,N'-diphenyl-1,3-propanediamine**,[3,4] $n^{25}D$ 1.6184, was obtained, with no evidence of 1-phenylazetidine formation.

B. 1,6-Dibromohexane. With *o*-Toluidine.—The procedure above gave **N,N'-di-(*o*-tolyl)-1,6-hexanediamine**, b.p. 183–185° at 0.1 mm., m.p. 45–47°, in 54% yield.

Anal. Calcd. for $C_{20}H_{28}N_2$: C, 81.03; H, 9.52; N, 9.45. Found: C, 81.31; H, 9.56; N, 9.68.

The dihydrochloride salt melted at 241–242°.

Anal. Calcd. for $C_{20}H_{30}Cl_2N_2$: N, 7.59. Found: N, 7.52.

With Aniline.—After a mixture of one mole of 1,6-dibromohexane and five moles of aniline was heated for two hours on the steam-bath, the solid product was treated with excess 10% sodium hydroxide and shaken with ether. By distillation of the extract there was obtained 2.6 moles of aniline and 0.52 mole of **N,N'-diphenyl-1,6-hexanediamine**,[5] b.p. 189° (0.1 mm.), m.p. 73–75°.

C. 1,4-Dibromobutane, 1,4-Dibromopentane and 2,5-Dibromohexane.—The reaction of these dibromoalkanes with ring-substituted anilines followed this general procedure. A mixture of dibromide (1 mole) and amine (3 to 5 moles) was heated on the steam-bath for one to two hours. Usually the amine hydrobromide separated as a crystalline solid and the mixture was diluted with ether and filtered. If there was no clean separation of starting material hydrobromide, the reaction mixture was treated with excess aqueous sodium hydroxide and then shaken with benzene. After distillation of the ether filtrate or the benzene extract, the higher boiling fraction containing 1-arylpyrrolidine and a small amount of recovered aniline was shaken with benzoyl chloride and aqueous sodium hydroxide to remove the latter. The products were obtained after extraction with benzene and redistillation in the yields given by Table 1, which also summarizes the physical properties and analyses of the bases and their picrate and hydrochloride salts.

By distillation of the residue from the first fractionation of 1-(*o*-tolyl)-2-methylpyrrolidine, **N,N'-di-(*o*-tolyl)-1,4-pen-**

tanediamine (IVa) was obtained in 1 to 2% yield as an oil boiling at 160–162° at 0.1 mm., $n^{25}D$ 1.5829.

Anal. Calcd. for $C_{19}H_{26}N_2$: C, 80.80; H, 9.28; N, 9.92. Found: C, 80.53; H, 9.18; N, 9.81.

The dihydrochloride salt, precipitated from alcohol by addition of dry ether, melted at 207–208°.

Anal. Calcd. for $C_{19}H_{28}Cl_2N_2$: C, 64.22; H, 7.94; N, 7.89. Found: C, 64.51; H, 8.06; N, 7.71

Scholtz and Friemehlt[8] describe this diamine IVa, which was their only product, as having the improbably low boiling point 191–193° at 23 mm.[25] When we carried out the reaction according to their method in alcohol, we isolated only 1-(*o*-tolyl)-2-methylpyrrolidine (IIIa) as product.

Derivatives of 1-Methoxyphenylpyrrolidines

A solution of 1.8 g. of 1-(2-methoxyphenyl)-pyrrolidine in 25 cc. of 48% hydrobromic acid was heated at reflux for 17 hours and then evaporated. The residual solid was taken up in alcohol, the solution evaporated, and the residue washed well with anhydrous ether to give 2.5 g. of **1-(2-hydroxyphenyl)-pyrrolidine hydrobromide.** A sample was recrystallized from alcohol, m.p. 170–171°, and the remainder of the salt was converted by one equivalent of aqueous sodium hydroxide to 1.6 g. of **1-(2-hydroxyphenyl)-pyrrolidine**, m.p. 108–109°. A sample which was sublimed for analysis melted unchanged.

Treatment of this base with methyl iodide in acetone gave **1-methyl-1-(2-hydroxyphenyl)-pyrrolidinium iodide**, an oil which was crystallized from alcohol and ether and which melted at 131–132°.

Anal. Calcd. for $C_{11}H_{16}INO$: C, 43.29; H, 5.29; N, 4.59. Found: C, 43.48; H, 5.50; N, 4.60.

Treatment of the base with dimethylcarbamyl chloride in pyridine, evaporation of the solvent, and addition of aqueous sodium hydroxide gave an oil which was distilled. There was obtained 57% of **1-(2-dimethylcarbamyloxyphenyl)-pyrrolidine** which boiled at 131° at 0.1 mm., $n^{25}D$ 1.5637.

Two forms of the **picrate** salt of this carbamate were isolated. When an ethereal solution of the base was treated with picric acid, there formed, besides an oil, a clump of long needles, m.p. 113–114°.

Anal. Calcd. for $C_{19}H_{21}N_5O_9$: C, 49.24; H, 4.57; N, 15.11. Found: C, 49.56; H, 4.82; N, 14.88.

Another sample of base was similarly treated, and the solid obtained was recrystallized from alcohol and ether mixture. It melted at 146–147°.

Anal. Found: C, 49.89; H, 4.68; N, 15.56.

A mixture of the two forms melted at 146–147°, as did a sample of the lower melting form after recrystallization and seeding with higher melting material.

A solution of the base and methyl iodide in dry acetone was heated to reflux for 16 hours, and the solvent was then removed. When the residual oil was allowed to stand under dry ether, it formed crystalline **1-methyl-1-(2-dimethylcarbamyloxyphenyl)-pyrrolidinium** iodide, m.p. 142–143°.

Anal. Calcd. for $C_{14}H_{21}IN_2O_2$: C, 44.69; H, 5.63; N, 7.45. Found: C, 45.07; H, 5.88; N, 8.03.

The other phenolic pyrrolidines described in Table I were obtained by similar procedures from the corresponding methyl ethers.

Reactions of α,α'-Dibromo-*o*-xylene

With Aniline.—A mixture of 9.3 g. (0.1 mole) of aniline and 7.6 g. (0.029 mole) of α,α'-dibromo-*o*-xylene became hot and formed a damp solid. This was heated with 70 cc. of benzene and the mixture was filtered giving 10 g. of aniline hydrobromide. Concentration of the filtrate and recrystallization gave 3.5 g. (62%) of **2-phenylisoindoline**, m.p. 172–173°.[11,22,26]

With *o*-Toluidine.—When *o*-toluidine and α,α'-dibromo-*o*-xylene in 3.5 to 1 molar proportions were heated together on a steam-bath for one-half hour and worked up with aqueous sodium hydroxide, there was obtained a 43% yield of 2-*o*-tolylisoindoline (VIa), an oil boiling at 117–120° at 0.1 mm., $n^{25}D$ 1.6200.

Anal. Calcd. for $C_{15}H_{15}N$: C, 86.08; H, 7.23; N, 6.69. Found: C, 86.37; H, 7.54; N, 6.81.

The hydrochloride salt melted at 151–152°.

Anal. Calcd. for $C_{15}H_{16}ClN$: C, 73.31; H, 6.56; N, 5.70. Found: C, 72.99; H, 6.74; N, 5.85.

The picrate melted at 145–146°.

Anal. Calcd. for $C_{21}H_{18}N_4O_7$: N, 12.78. Found: N, 12.76.

Treatment of the base with methyl iodide in refluxing acetone gave crystals of **2-methyl-2-*o*-tolylisoindolinium iodide**, m.p. 176–178°, in 76% yield.

Anal. Calcd. for $C_{16}H_{18}IN$: C, 54.71; H, 5.17. Found: C, 54.91; H, 5.21.

The residue from the distillation of 2-*o*-tolylisoindoline was crystallized from a mixture of benzene and Skellysolve B and then from alcohol. **N,N'-Di-(*o*-tolyl)-α,α'-diamino-*o*-xylene (VIIa)**,[11] m.p. 145°, was obtained in about 5% yield.

Anal. Calcd. for $C_{22}H_{24}N_2$: C, 83.50; H, 7.65; N, 8.86. Found: C, 83.85; H, 7.44; N, 8.86.

When this reaction was carried out in chloroform[11] and the filtrate after removal of *o*-toluidine hydrobromide was distilled, there was obtained a 77% yield of 2-*o*-tolylisoindoline. Crystallization of the residue from benzene–Skellysolve B mixture gave 6% of N,N'-di-(*o*-tolyl)-α,α'-diamino-*o*-xylene.

With *o*-Anisidine.—The procedure is that of Scholtz.[11] A solution of 12.3 g. (0.1 mole) of *o*-anisidine and 6.6 g. (0.025 mole) of α,α'-dibromo-*o*-xylene in 100 cc. of 95% alcohol was refluxed for one-half hour, and then concentrated to about 50-ml. volume. The residue was poured into 200 ml. of water and the mixture was shaken twice with ether. From the aqueous layer was obtained 4.5 g. of recovered *o*-anisidine. The combined ether extracts were distilled and gave 3 g. (54%) of **2-(2-methoxyphenyl)-isoindoline (VIb)**, b.p. 134–137° at 0.1 mm., $n^{25}D$ 1.6247.

Anal. Calcd. for $C_{15}H_{15}NO$: C, 79.97; H, 6.71. Found: C, 79.83; H, 6.45.

The hydrochloride salt formed crystals in ether and melted at 180–183°.

Anal. Calcd. for $C_{15}H_{16}ClNO$: C, 68.82; H, 6.16. Found: C, 69.05; H, 6.30.

The picrate melted at 131°.

Anal. Calcd. for $C_{21}H_{18}N_4O_8$: N, 12.33. Found: N, 12.46.

2-Methyl-2-(2-methoxyphenyl)-isoindolinium iodide was prepared in acetone in 74% yield, and melted at 150–152°.

Anal. Calcd. for $C_{16}H_{18}INO$: C, 52.33; H, 4.94. Found: C, 52.41; H, 5.04.

Crystallization in alcohol of the residue from the distillation gave 2 g. (23%) of **N,N'-di-(2-methoxyphenyl)-α,α'-diamino-*o*-xylene (VIIb)**,[11] m.p. 105–106°.

Anal. Calcd. for $C_{22}H_{24}N_2O_2$: N, 8.04. Found: N, 8.15.

A yield of 58% of the isoindoline VIb was obtained when no solvent was used for the reaction.

A solution of 3.3 g. of 2-(2-methoxyphenyl)-isoindoline in 50 ml. of 48% hydrobromic acid was refluxed 16 hours and cooled, and 3.4 g. (79%) of **2-(2-hydroxyphenyl)-isoindoline hydrobromide**, m.p. 226–229°, was obtained.

Anal. Calcd. for $C_{14}H_{14}BrNO$: C, 57.55; H, 4.83; N, 4.79. Found: C, 57.63; H, 5.05; N, 4.91.

The free base **2-(2-hydroxyphenyl)-isoindoline**, prepared by neutralization of a solution of the hydrobromide salt, was recrystallized from Skellysolve B. It formed white needles melting at 118–119°.

Anal. Calcd. for $C_{14}H_{13}NO$: C, 79.59; H, 6.20; N, 6.63. Found: C, 79.58; H, 6.09; N, 6.75.

The picrate of this base melted at 154–155°.

Anal. Calcd. for $C_{20}H_{16}N_4O_8$: N, 12.72. Found: N, 12.48.

2-Methyl-2-(2-hydroxyphenyl)-isoindolinium iodide formed fine crystals, m.p. 180–181°, in acetone.

Anal. Calcd. for $C_{15}H_{16}INO$: C, 51.00; H, 4.57. Found: C, 51.16; H, 4.99.

With 2,6-Dimethylaniline.—A mixture of 24.3 g. (0.2 mole) of 2,6-dimethylaniline and 13.2 g. (0.05 mole) of

(25) In contrast, in ref. 3 Scholtz gives b.p. 280–285° at 16 mm. for N,N'-diphenyl-1,3-diaminopropane.

(26) S. Sugasawa and K. Kodama, *J. Pharm. Soc. Japan*, **63**, 96 (1943); *C. A.*, **45**, 5168 (1951).

α,α'-dibromo-*o*-xylene was warmed, and soon gave a clear brown oil with heat evolution. This oil formed a crystalline solid which was heated on the steam-bath for one hour, after which 125 cc. of benzene was added and heating continued for one-half hour. The mixture was filtered, and the filtrate was distilled giving 5.7 g. of crude **2-(2,6-dimethylphenyl)-isoindoline (VIc)**, b.p. 100–120° at 0.1 mm., which was recrystallized from 50 cc. of 95% ethanol as 3.6 g. (33%) of white needles, m.p. 58–59°. This base, which is very soluble in hydrocarbons, soon darkened and became oily on standing in air.

Anal. Calcd. for $C_{16}H_{17}N$: C, 86.05; H, 7.68; N, 6.27. Found: C, 85.73; H, 7.30; N, 6.44.

When converted to the **hydrochloride** salt in dry ether, it gave white needles melting at 168–174°.

Anal. Calcd. for $C_{16}H_{18}ClN$: N, 5.39. Found: N, 5.36.

When the base was heated with methyl iodide in acetone, white needles of **2-methyl-2-(2,6-dimethylphenyl)-isoindolinium iodide** formed which melted at 211–212°.

Anal. Calcd. for $C_{17}H_{20}IN$: C, 55.90; H, 5.52; N, 3.84. Found: C, 54.81; H, 5.20; N, 4.02.

The white crystalline residue from the filtration was dissolved in hot water and cooled to give 3.9 g. (15%) of **N,N'-bis-(2,6-dimethylphenyl)-α,α'-diamino-*o*-xylene dihydrobromide hemihydrate** as white crystals, m.p. 172–173°.

Anal. Calcd. for $C_{24}H_{28}N_2 \cdot 2HBr \cdot 0.5H_2O$: C, 55.92; H, 6.06; N, 5.44. Found: C, 55.71; H, 6.12; N, 5.44.

This salt was converted to the base **N,N'-bis-(2,6-dimethylphenyl)-α,α'-diamino-*o*-xylene (VIIc)**, an oil, $n^{25}D$ 1.6022, which was made free of solvent by heating in an oil-bath at 100° at 0.1 mm.

Anal. Calcd. for $C_{24}H_{28}N_2$: C, 83.67; H, 8.19; N, 8.13. Found: C, 84.31; H, 7.86; N, 8.04.

The dihydrochloride hemihydrate salt crystallized in ether and melted at 189°.

Anal. Calcd. for $C_{24}H_{28}N_2 \cdot 2HCl \cdot 0.5H_2O$: C, 67.59; H, 7.33; N, 6.57. Found: C, 67.83; H, 7.65; N, 6.54.

The dipicrate melted at 175° when recrystallized from alcohol.

Anal. Calcd. for $C_{36}H_{34}N_8O_{14}$: N, 13.96. Found: N, 13.79.

Reactions of 2-(β-Bromoethyl)-α-bromotoluene

With *o*-Toluidine.—A mixture of 16 g. (0.15 mole) of *o*-toluidine and 8.5 g. (0.03 mole) of 2-(β-bromoethyl)-α-bromotoluene[27] was heated on the steam-bath for one-half hour and, after addition of 100 ml. of benzene, for one hour longer under a reflux condenser. Filtration gave a solid from which 7.2 g. of *o*-toluidine was recovered by treatment with base. Two distillations of the filtrate gave an additional 3.4 g. of *o*-toluidine and 5.3 g. (79%) of **2-(*o*-tolyl)-1,2,3,4-tetrahydroisoquinoline (VIIIa)**, b.p. 133–135° at 0.25 mm., $n^{25}D$ 1.6016.

Anal. Calcd. for $C_{16}H_{17}N$: C, 86.05; H, 7.68; N, 6.27. Found: C, 86.37; H, 7.58; N, 6.70.

The picrate was recrystallized from alcohol and melted at 108°.

Anal. Calcd. for $C_{22}H_{20}N_4O_7$: N, 12.39. Found: N, 12.21.

With 2,6-Dimethylaniline.—By a procedure similar to that above, there was obtained a 52% yield of **2-(2,6-dimethylphenyl)-1,2,3,4-tetrahydroisoquinoline (VIIIb)**, a yellow oil, b.p. 120–125° at 0.1 mm., $n^{25}D$ 1.5915.

Anal. Calcd. for $C_{17}H_{19}N$: C, 86.03; H, 8.07; N, 5.90. Found: C, 85.33; H, 8.07; N, 5.99.

Attempts to prepare salts of this base gave only oils.

Compounds Derived from Phthalic Anhydride

2-(2,6-Dimethylphenyl)-phthalimide (IX), prepared by heating together phthalic anhydride and 2,6-dimethylaniline at 180° for two hours, melted at 204° as reported by Vanags.[17]

N-(2,6-Dimethylphenyl)-phthalamic Acid (XI).—A solution of 22 g. (0.15 mole) of phthalic anhydride in 190 cc. of glacial acetic acid was cooled to 25° and 12.1 g. (0.1 mole) of 2,6-dimethylaniline was added. The temperature rose to 36° and a solid separated. After 15 minutes, the mixture was cooled to 30° and filtered. The white solid was washed with acetic acid and then with water. It weighed 24 g. (89%) and melted at 188–189°, unchanged by crystallization from alcohol. It was completely soluble in dilute aqueous sodium hydroxide.

Anal. Calcd. for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.62; N, 5.20; O, 17.82. Found: C, 71.31; H, 5.72; N, 5.17; O, 17.76.

When a sample of this acid was heated at 200° for two hours, the base-insoluble imide IX, m.p. 203–204°, was formed.

Reduction of 2-(2,6-Dimethylphenyl)-phthalimide (IX).—By extraction from a Soxhlet apparatus, 10 g. (0.04 mole) of imide was added to a solution of 3.1 g. (0.08 mole) of lithium aluminum hydride in 0.5 liter of refluxing dry ether with stirring under nitrogen. After four hours, the mixture was hydrolyzed by the addition of 3 cc. of water, 3 cc. of 15% potassium hydroxide and 9 cc. of water. The white suspension was filtered, and the inorganic solid was washed well with dry ether. Evaporation of the filtrate gave 7 g. of solid which was stirred with pentane. There remained undissolved 2.4 g. of white solid which was removed. The filtrate was distilled to give 4.4 g. (50%) of 2-(2,6-dimethylphenyl)-isoindoline (VIc), distilling at 104–110° at 0.1 mm., m.p. 56–58°. Although this material seemed more stable when kept in a closed receiver than that which was prepared from the dibromide, it too darkened and became oily on exposure to air. The white solid from the filtration was triturated with 75 cc. of hot Skellysolve B which left undissolved 2.3 g. (23%) of **N-(2,6-dimethylphenyl)-2-hydroxymethylbenzamide (X)**, m.p. 145°, unchanged by crystallization from benzene.

Anal. Calcd. for $C_{16}H_{17}NO_2$: C, 75.26; H, 6.71; N, 5.49. Found: C, 75.11; H, 6.94; N, 5.43.

By warming 0.15 g. of this alcohol with 0.9 cc. of phenylisocyanate there was obtained **N-(2,6-dimethylphenyl)-2-(phenylcarbamyloxymethyl)-benzamide**, which crystallized in alcohol as white needles, m.p. 196–198°.

Anal. Calcd. for $C_{23}H_{22}N_2O_3$: N, 7.48. Found: N, 7.48.

Reduction of N-(2,6-Dimethylphenyl)-phthalamic Acid (XI).—The technique described above was used except that about 20 hours was required to dissolve 10.8 g. (0.04 mole) of the acid in the Soxhlet device. The hydrolyzed mixture was filtered and the residue was stirred with dilute sulfuric acid, which left undissolved 3.9 g. of N-(2,6-dimethylphenyl)-2-hydroxymethylbenzamide (X). Evaporation of the ether filtrate and trituration of the residue with 100 cc. of hot Skellysolve B left 3.8 g. additional amide X, m.p. 143–144°, a total yield of 75%.

From the Skellysolve by concentration and cooling was obtained 1.2 g. (12%) of **N-(2,6-dimethylphenyl)-2-hydroxymethylbenzylamine (XII)**, white cubes which melted at 101–102° after recrystallization from 70% alcohol.[28]

Anal. Calcd. for $C_{16}H_{19}NO$: C, 79.63; H, 7.94; N, 5.81. Found: C, 79.84; H, 7.94; N, 5.89.

The hydrochloride salt of this amino alcohol melted at 209–210°.

Anal. Calcd. for $C_{16}H_{20}ClNO$: N, 5.04. Found: N, 5.31.

The picrate, recrystallized from water, melted at 160–161°.

Anal. Calcd. for $C_{22}H_{22}N_4O_8$: N, 11.91. Found: N, 12.09.

Reduction of N-(2,6-Dimethylphenyl)-2-hydroxymethylbenzamide (X).—The addition of 2.6 g. (0.01 mole) of the amide X to 0.8 g. (0.02 mole) of lithium aluminum hydride in 300 ml. of dry ether during 1.5 hours gave a conversion of about 13% of the amide to N-(2,6-dimethylphenyl)-2-hydroxymethylbenzylamine (XII), m.p. 101–102°, in a yield of 64%, based on unrecovered amide.

Compounds Derived from Homophthalic Anhydride

Reaction with *o*-Toluidine.—A mixture of 8.1 g. (0.05 mole) of homophthalic anhydride and 5.4 g. (0.05 mole) of

(27) E. L. Anderson and F. G. Holliman, *J. Chem. Soc.*, 1037 (1950).

(28) D. E. Sunko, *Arhiv Kem.*, **27**, 183 (1955), has recently reported the reduction of a phthalamic acid which yielded a similar mixture of products.

o-toluidine was heated to 183° in 0.5 hour, cooled, and triturated with 75 cc. of hot Skellysolve C. The decanted solvent yielded 1.0 g. of **2-(*o*-tolyl)-1,2,3,4-tetrahydro-1,3-isoquinolinedione (XIII)**, a crystalline solid, m.p. 103–106°, which was soluble in aqueous alkali.

Anal. Calcd. for $C_{16}H_{13}NO_2$: C, 76.48; H, 5.21; N, 5.56. Found: C, 76.39; H, 5.37; N, 5.59.

The residual gum was triturated with 75 ml. of hot benzene and the mixture was filtered. In the filtrate formed 0.3 g. of **N-(*o*-tolyl)-2-carboxyphenylacetamide (XIV)**, fine white crystals which melted at 183–184°.

Anal. Calcd. for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.62; N, 5.20. Found: C, 71.47; H, 5.68; N, 5.10.

Reaction with 2,6-Dimethylaniline.—A mixture of 16.2 g. (0.1 mole) of homophthalic anhydride and 12.1 g. (0.1 mole) of 2,6-dimethylaniline was heated at about 150° for 30 minutes. The original melt formed a hard solid which was triturated with ethanol and with dioxane. The crystals of **N-(2,6-dimethylphenyl)-2-carboxyphenylacetamide (XV)** which formed in the filtered solvent weighed 16 g. (57%) and melted at 235–237°.

Anal. Calcd. for $C_{17}H_{17}NO_3$: C, 72.06; H, 6.05; N, 4.94. Found: C, 71.75; H, 6.13; N, 4.95.

Reduction of N-(2,6-Dimethylphenyl)-2-carboxyphenylacetamide (XV).—A solution of 1.6 g. (0.04 mole) of lithium aluminum hydride in 0.5 liter of dry ether was treated with 5.7 g. (0.02 mole) of this amide XV and the mixture worked up as described for the homologous amide XI. There was obtained 2 g. (37%) of **N-(2,6-dimethylphenyl)-2-hydroxymethylphenylacetamide (XVII)**, an acid-insoluble solid which was recrystallized from alcohol and melted at 150–151°.

Anal. Calcd. for $C_{17}H_{19}NO_2$: C, 75.81; H, 7.11; N, 5.20; O, 11.88. Found: C, 76.02; H, 7.45; N, 5.27; O, 12.03.

The acid-soluble material in the residue from the evaporation of the ether extract was dissolved in dilute hydrochloric acid which was then shaken with benzene. The aqueous layer was basified with aqueous sodium hydroxide and the oil was extracted in benzene. Distillation gave 0.8 g. (16%) of **N-(2,6-dimethylphenyl)-2-hydroxymethyl-β-phenylethylamine (XVI)**, a fluorescent oil, b.p. 150–153° at 0.1 mm., $n^{25}D$ 1.5870.

Anal. Calcd. for $C_{17}H_{21}NO$: C, 79.96; H, 8.29; N, 5.49. Found: C, 79.99; H, 8.47; N, 5.53.

The hydrochloride salt formed in ether as colorless prisms, m.p. 185–186°.

Anal. Calcd. for $C_{17}H_{22}ClNO$: C, 69.96; H, 7.60. Found: C, 70.29; H, 7.44.

N-(2,6-Dimethylphenyl)-*o*-tolylacetamide (XVIII). Method A.—A solution of 1.3 g. of 2,6-dimethylaniline and 1.1 g. of triethylamine in 40 ml. of dry benzene was treated with 1.7 g. of *o*-tolylacetyl chloride, and the mixture was heated on steam for 0.5 hour and filtered hot. In the cooled filtrate separated 2 g. of solid which was recrystallized from 95% alcohol and from Skellysolve C. It formed fine white needles, m.p. 192°.

Anal. Calcd. for $C_{17}H_{19}NO$: C, 80.59; H, 7.56; N, 5.53. Found: C, 80.56; H, 7.71; N, 5.63.

Method B.—A solution of 1 g. of N-(2,6-dimethylphenyl)-2-hydroxymethylphenylacetamide (XVII) in alcohol was shaken over palladized charcoal under 30 lb. pressure of hydrogen until absorption was complete. The solution was filtered and the filtrate evaporated to obtain 0.9 g. of white solid, m.p. 192°. A sample recrystallized from Skellysolve C melted at 193°, not depressed by mixture with material prepared by method A.

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[CONTRIBUTION FROM THE BIOCHEMISTRY DEPARTMENT, COLLEGE OF PHYSICIANS AND SURGEONS, COLUMBIA UNIVERSITY, AND THE FRANCIS DELAFIELD HOSPITAL]

Some New Benzimidazoles and Quinoxalines

BY H. B. GILLESPIE, MORRIS ENGELMAN AND SAMUEL GRAFF

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Growth antagonism by substituted benzotriazoles and benzimidazoles has been reported in earlier papers. 4-Methoxy-6-nitrobenzimidazole was found to be one of the most potent of the compounds studied. In order to pin-point the biological effect of groups, position of these groups and ring size, a number of modifications of 4-methoxy-6-nitrobenzimidazole were required. Accordingly, 2-substituted 4-methoxy-6-nitrobenzimidazoles, derivatives of 6-methoxy-4-nitrobenzimidazole and 5-methoxy-7-nitroquinoxaline were prepared for biological investigation.

A number of nitro and methoxy substituted benzotriazoles and benzimidazoles antagonize growth and/or development of certain biological species.[1,2] The systems investigated include *Tetrahymena geleii*[3] (a guanine-requiring protozoan), several strains of *Escherichia coli*,[3] and developing frog embryos (*Rana pipiens*).[4] The latter have been found to be sensitive to concentrations of these compounds below 0.002%. Accordingly, modifications of 4-methoxy-6-nitrobenzimidazole were prepared in which the structure of the benzene ring was maintained but substituents were placed on the 2-position (*i.e.* on the imidazole ring). Expanding the imidazole ring to a six-membered ring gave a series of quinoxalines and derivatives. Another group of compounds was prepared in which the methoxy and nitro groups were interchanged. Thus three general types of compounds are reported here: (A) 2-substituted 4-methoxy-6-nitrobenzimidazoles and derivatives, (B) 5-methoxy-7-nitroquinoxalines and derivatives and (C) derivatives of 6-methoxy-4-nitrobenzimidazole[5] and 7-methoxy-5-nitroquinoxaline.[6]

The 2-substituted 4-methoxy-6-nitrobenzimidazoles were prepared from 2,3-diamino-5-nitroanisole. Condensation of the diamine with acetic acid or urea yielded, respectively, the 2-methyl (I) and the 2-hydroxybenzimidazole (V). The 6-amino

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(3) S. B. Greer, *Soc. Am. Bacteriologists*, New York Meeting, Jan. 6, 1954.

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(5) F. E. King, R. J. S. Beer and S. G. Waley, *J. Chem. Soc.*, 94 (1946).

(6) R. H. Mizzoni and P. E. Spoerri, THIS JOURNAL, **67**, 1653 (1945).