2,2,3-Triarylpropionitriles and Related Compounds as Hypocholesterolemic Agents

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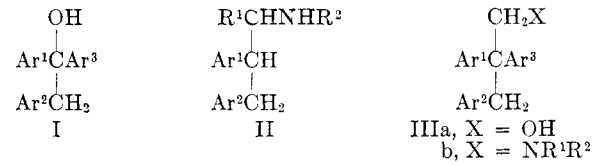
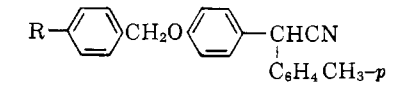
Various 2,2,3-triarylpropyl compounds were prepared and evaluated in rats for cholesterol lowering activity. The 2,2,3-triarylpropionitriles were found to have marked hypocholesterolemic activity at low dosage levels. A discussion of the preparation, n.m.r. spectra, and pharmacology of these compounds is presented.

Among the several types of compounds for which serum cholesterol lowering activity has been demonstrated in man are triparanol,[1] 1-[p-(β-diethylaminoethoxy)phenyl]-1-(*p*-tolyl)-2-(*p*-chlorophenyl)ethanol (represented by general formula I), and benzmalecene,[2] N-(1-methyl-2,3-di-*p*-chlorophenylpropyl)-maleamic acid (represented by general formula II). Consideration of the structural similarity of the triarylethanol I and the diarylpropylamine II suggested the value of synthesizing a hybrid system of triarylpropanols (IIIa) and triarylpropylamines (IIIb) for screening as hypocholesterolemic agents. As it developed, several triarylpropionitriles prepared as intermediates for the synthesis of compounds of type III are of considerably more pharmacologic interest than either IIIa or IIIb.[3]

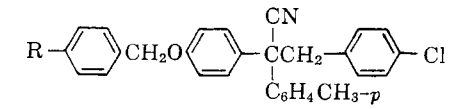


I II IIIa, X = OH; b, X = NR^1R^2

The general synthetic route which provided all of the compounds under discussion is illustrated by the example in Chart I. *p*-Benzoyloxybenzaldehyde (IV) was converted to the diarylacetonitrile V by treatment with boron trifluoride, hydrogen cyanide, and toluene.[4] An attempt to alkylate V on the α-carbon by means of sodamide and *p*-chlorobenzyl chloride led instead to the ether XIVa. Realkylation of XIVa then gave the expected Cα-alkylation product XVa. Although the *p*-chlorobenzyl ether in XVa could undoubtedly have been cleaved and the resulting phenol alkylated to the

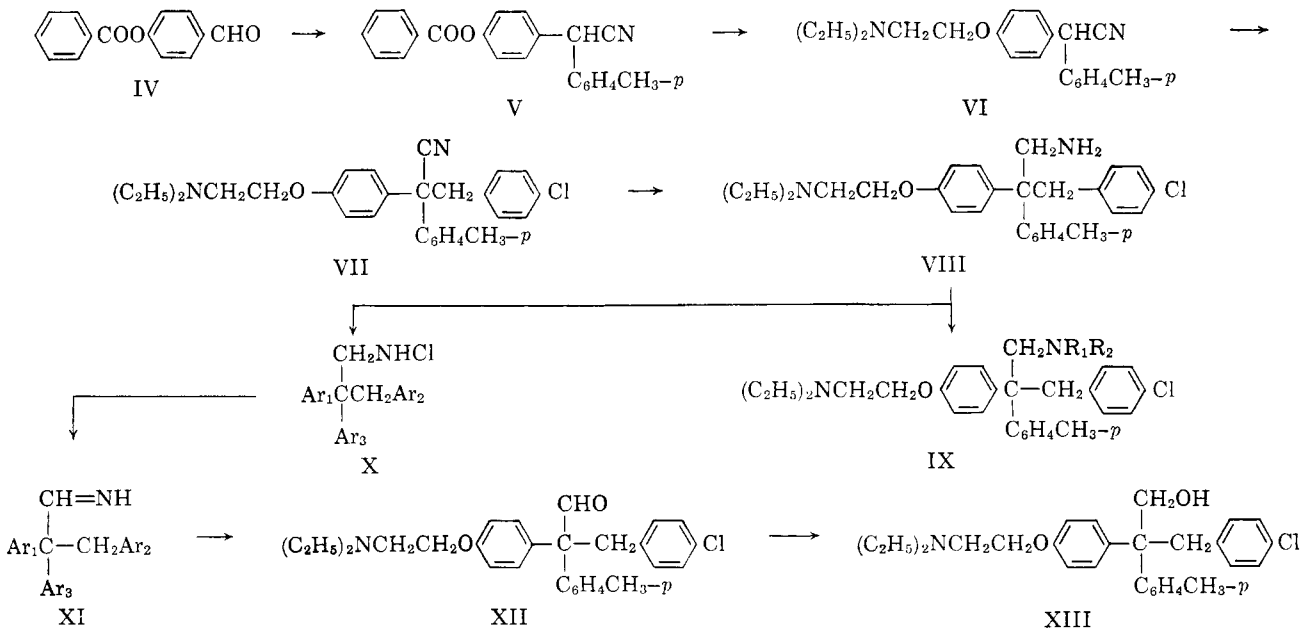


XIVa, R = Cl
b, R = H



XVa, R = Cl
b, R = H

CHART I



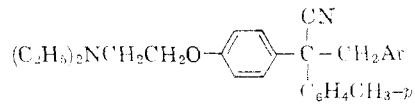
(1) Progress in Cardiovascular Diseases, Vol. II, No. 6 (Part I), May, 1960. Proceedings of the Conference on MER-29 (Triparanol).

(2) S. S. Bergen, Jr., L. B. Van Itallie, and W. H. Sebrell, *Proc. Soc. Exptl. Biol. Med.*, **103**, 39 (1960). R. H. Furman, R. P. Howard, L. N. Norica and C. W. Robinson, Jr., *Proc. Soc. Exptl. Biol. Med.*, **103**, 302 (1960). B. A. Sachs, E. Danielson, and R. J. Sperber, *Metab. Clin. Exp.*, **9**, 783 (1960).

(3) A recent report indicated that some 2,3-diarylacrylonitriles substituted with the diethylaminoethyl ether function were found to have cholesterol lowering activity in rats. These compounds were reportedly made on the basis of analogies to the stilbestrol structure and the known hypocholesterolemic effect of many estrogenic substances. G. M. K. Hughes, P. F. Moore, and R. B. Stebbins, paper No. 14, and S. K. Figdor, E. C. Schreiber, R. B. Stebbins, P. F. Moore, and R. Punson, Jr., paper No. 15, Abstracts of the 142nd National Meeting of the American Chemical Society, Medicinal Section, Atlantic City, N. J., September 9–14, 1962. Also, *Chem. Eng. News*, **40**, 54 (September 17, 1962).

(4) J. Mills, U.S. Patent 2,447,419 (August 11, 1947).

TABLE I



Compound	Ar	Method[a]	Yield pure, %	pKa[b]	Molecular weight Calcd.	Found	M.p., °C.	Solvent
VII·HCl	*p*-ClC_6H_4-	t, n	53.0	8.05	484	483	168–172	EtOAc
XX	4-Pyridyl	n[b]	57.0	8.02	414	443		Oily
XXI·oxalate	C_6H_5-	n[b,c]	60.5	8.10	412	428	140–150	EtOAc
XXII·HCl	*p*-$(CH_3O)C_6H_4$-	n	93.0	8.05	479	484	175–178	EtOAc
XXIII	*o*-ClC_6H_4-	t[c]	45.5	8.35	447	467		Oily
XXIV·oxalate	*m*-ClC_6H_4-	t	42.4	8.20	537	539	134	EtOAc–Et_2O
XXV·HCl	3,4-$Cl_2C_6H_3$-	n	83.0	7.90	518	508	143–147 201–203	EtOAc–acetone
XXVI·HCl	2,4-$Cl_2C_6H_3$-	n	72.5	7.88	518	522	164–166	EtOAc
XXVII·HCl	*p*-$(NO_2)C_6H_4$-	n	58.0	8.15	494	487	160–162	EtOAc–acetone
XXVIII·HCl	*m*-$(NO_2)C_6H_4$-	n	57.0	8.15	494	500	158–162	EtOAc
XXIX·HCl	*p*-$(CF_3)C_6H_4$-	n	74.0				145–146	EtOAc
XXX·HCl	*p*-FC_6H_4-	n	78.5	8.10	467	470	144–148	EtOAc
XXXI·HCl	*p*-$(CH_3)C_6H_4$-	n	74.0	8.30	462	472	159–162	EtOAc–Et_2O
XXXII·oxalate	C_6H_{11}-	t[c]	39.2				69–71	EtOAc

[a] t = compound prepared by alkylation in toluene solvent by procedure similar to that reported for XIVa. n = compound prepared by alkylation in liquid ammonia by procedure similar to that reported for XVb. [b] The free base was purified by chromatography on alumina. [c] Although XXIII and XXXII were purified as the hygroscopic oxalate, the analyses and pharmacologic testing was done on

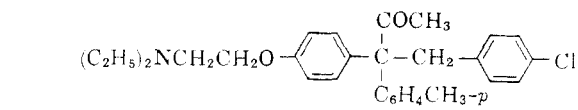
desired amino ether VII, this was not the route employed in preparing quantities of the various analogs of VII. The ether cleavage and subsequent alkylation to an aminoether actually was carried out, but on XVb, the benzyloxy analog of XVa (see Experimental). In addition, attempts to synthesize XIVb directly, by using *p*-benzyloxybenzaldehyde in place of IV, led only to red, viscous oils and gums. The formation of XIVa was readily avoided by converting V to the amino ether VI before the sodamide-*p*-chlorobenzyl chloride alkylation reaction. In this manner VII, and its homologs and analogs, could be obtained in three steps and good yield. When toluene was used as the solvent in the alkylation step, appreciable amounts (10–30%) of quaternary amines were formed and purifications sometimes became laborious. The use of liquid ammonia as the solvent minimized amine quaternization (<5%) and usually allowed purification by direct crystallization of a salt of the aminonitriles.

The IIIb-type amines were then obtained by lithium-aluminum hydride reduction of VII to VIII). Compound VIII served for the preparation of a few N-substituted and N,N-disubstituted compounds (IX).

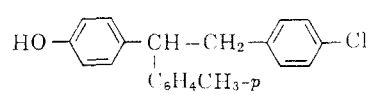
The original plan for the preparation of the IIIa-type propanols, *e.g.*, XIII, involved the hydrolysis of VII to the corresponding amide, ester, or acid and subsequent conversion to XIII. Attempts to hydrolyze the nitrile group in VII proved fruitless although hydrolysis does succeed with somewhat similar systems in the analgesic field.[5] In view of these difficulties, a 5-step conversion of VII to XIII which proceeds *via* the amine VIII was employed.[6] The process was vastly facilitated by the fact that purification of the reaction products was unnecessary until isolation of the final product (XIII). Upon one occasion, however, a sample of the aldehyde XII was purified for physicochemical analysis and pharmacologic testing. Successful conversion of VIII to the chloramine X with N-chlorosuccinimide could be determined by examination of the infrared spectrum of the crude reaction product. The chloramine N–H peak occurs at 3.04 μ shifted from the 2.94 μ peak of the amine VIII. Base treatment of X yielded the imine XI which was not isolated but immediately hydrolyzed to the aldehyde XII. Lithium aluminum hydride reduction of XII then gave the propanol XIII.

Cholesterol synthesis inhibition studies in rat liver tissue in an *in vitro* incubation system indicated that the

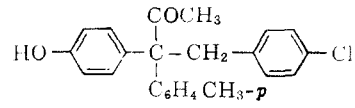
(5) "Synthetic Analgesics," Part I, P. A. J. Janssen, Pergamon Press, Inc., New York, N. Y., 1960, Chapters IX, X, and XIII. Conditions sufficiently vigorous to give indications of amide formation also caused extensive charring, cleavage of the ether function, or sulfonation of the phenolic ring when sulfuric acid was used as the hydrolytic reagent. Another example of the hindered nature of the nitrile resulted from studies of the reaction of VII with excess CH_3MgBr. To illustrate, 2.76 g. of VII was treated with CH_3MgBr in refluxing toluene for 4.5 hr. Chromatography of the hydrolyzed ketimine mixture gave 115 mg. of the desired ketone (i), 315 mg. of descyanophenol (ii), and about 1 g. of crude phenolic ketone (iii). *Cf.* "Synthetic Analgesics," Part I, Chapter XVI. More gentle treatment of



i



ii



iii

VII (toluene, 2 hr., 80°) gave only starting material. Somewhat similar results were obtained upon treatment of XVb with excess methyl Grignard reagent in toluene. No reaction occurred after heating the mixture 4 hr. at 60–80°. Heating at reflux temperature (6 hr.) caused extensive benzyl ether cleavage and reductive removal of the cyano group along with formation of some methyl ketone.

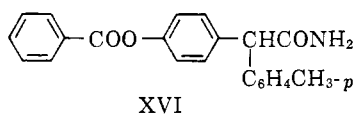
(6) This general process was used by H. Ruschig, W. Fritsch, J. Schmidt-Thome, and W. Haede, *Chem. Ber.*, **88**, 883 (1955), for the conversion of steroidal 20-amines to 20-ketones. It was subsequently used to convert several steroidal alkaloids to nitrogen-free steroids.

Formula	Analyses							
	Calcd.				Found			
	C	H	Cl	N	C	H	Cl	N
$C_{28}H_{31}ClN_2O \cdot HCl$	69.55	6.67	14.67	5.79	69.46	6.84	14.76	6.02
$C_{27}H_{31}N_3O$	78.41	7.56		10.16	77.64	7.38		10.07
$C_{28}H_{32}N_2O \cdot C_2H_2O_4$	71.69	6.82		5.57	71.24	6.91		5.31
$C_{29}H_{34}N_2O_2 \cdot HCl$	72.70	7.36	7.40	5.85	72.12	7.48	7.64	5.60
$C_{28}H_{31}ClN_2O$			7.93				7.97	
$C_{28}H_{31}ClN_2O \cdot C_2H_2O_4$	67.09	6.19	6.60	5.22	66.54	6.22	6.50	4.79
$C_{28}H_{30}Cl_2N_2O \cdot HCl$	64.93	6.03	20.54	5.41	65.58	6.28	20.24	5.37
$C_{28}H_{30}Cl_2N_2O \cdot HCl$	64.93	6.03	20.54	5.41	64.96	6.33	20.26	5.24
$C_{28}H_{31}N_3O_3 \cdot HCl$	68.07	6.53	7.18	8.51	68.06	6.74	7.26	8.42
$C_{28}H_{31}N_3O_3 \cdot HCl$	68.07	6.53	7.18	8.51	67.83	6.69	7.07	8.25
$C_{29}H_{31}F_3N_2O \cdot HCl$[f]	67.36	6.24	6.86	5.42	67.07	6.37	6.85	5.27
$C_{28}H_{31}FN_2O \cdot HCl$[g]	72.01	6.91	7.59	6.00	71.73	7.06	7.64	5.88
$C_{29}H_{34}N_2O \cdot HCl$	75.22	7.62		6.05	75.31	7.79		5.62
$C_{28}H_{33}N_2O$	80.33	9.15		6.69	80.25	9.19		6.74

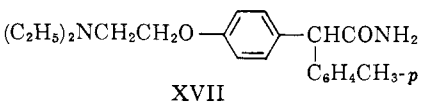
the free base. [d] The titration was performed on the oily free base. [e] In this alkylation the aminonitrile (VI) was added to the reaction as the hydrochloride and two equivalents of sodamide were employed. The results were comparable to the use of the free base with one equivalent of sodamide. [f] F, calcd.: 11.02. Found: 11.89. [g] F, Calcd.: 4.07. Found: 4.15.

propanol XIII was less active than triparanol. The nitrile VII, on the other hand, was definitely more active. Comparable results were also obtained in animal experiments (*vide infra*). In addition, animal testing indicated that the aldehyde XII, and the amine VIII and several of its derivatives (IX: (a) R_1 = H, R_2 = $COCH_3$; (b) R_1 = H, R_2 = C_2H_5; (c) R_1 = CH_3, R_2 = C_2H_5; (d) R_1 = R_2 = CH_3) were without activity. In view of these results, the emphasis in the synthetic program was shifted to analogs of VII.

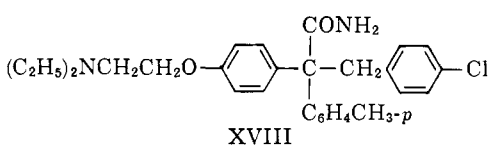
A large-scale preparation of nitrile V allowed the isolation of an amide by-product (XVI) in about 5% yield. Under the influence of the boron trifluoride catalyst, the water generated in the preparation of V had evidently hydrolyzed some of the nitrile to amide



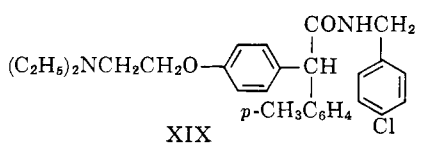
XVI



XVII



XVIII



XIX

XVI. Conversion of XVI to XVII could be effected without difficulty; however, amide XVII was more readily obtained by a carefully controlled hydrolysis of VI.

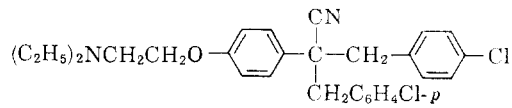
With XVII in hand, the possibility arose of synthesizing the triarylpropionamide XVIII, which we had not been able to obtain by hydrolyzing VII (*vide supra*). Although amides in which the nitrogen is not disubstituted are known to undergo N-alkylation in preference to alkylation on the α-carbon, the possibility existed that the two aryl functions in XVII might reverse the order of preference. The *p*-methyl and *p*-ether functions in XVII would, of course, exert a destabilizing effect upon the desired carbanion formation. Treatment of XVII with sodamide and *p*-chlorobenzyl chloride in toluene gave the amide XIX, the quaternary salt of XIX, and some starting material. None of the desired amide (XVIII) was detected. Efforts were then made to utilize the versatile dianion techniques of Hauser[7] in order to obtain C-alkylation. The use of 2 moles of sodamide or potassium amide in liquid ammonia gave color changes suggestive of dianion formation. Addition of one equivalent of *p*-chlorobenzyl chloride to the reaction mixture dissipated the orange color and regenerated the gray color characteristic of the amide monoanion. However, neither C- nor N-alkylation products was obtained. Rather than alkylating the carbanion, the benzyl halide evidently served as a proton source for the carbanion, and was itself converted to a stilbene. Thus, this method of obtaining triarylpropionamides was not successful.

Table I summarizes variations made in the C-3 aryl group of VII. Among these compounds, only XX and XXXII were without significant hypocholesterolemic activity. The remaining compounds were in general active orally in the dose range of <0.005–0.01% in

(7) R. B. Meyer and C. R. Hauser, *J. Org. Chem.*, **26**, 3696 (1961).

the diet.[8] Among the most active compounds were VII, XXI, XXII, XXIII, and XXIV. By the same assay method triparanol has borderline activity at 0.01% and definite activity at 0.02% in the diet. Given subcutaneously, the compounds were generally active at 1 or 3 mg./rat/day dose levels, although they did not appear as effective as triparanol in this test.[9]

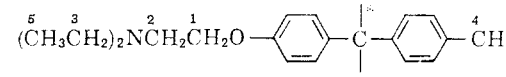
The propanol (XIII) was active only at 5 mg./rat/day, s.c., and orally at 0.10% in the diet. The necessity of the amine side chain for pharmacologic activity was demonstrated by the fact that ethers XVa and XVb and the corresponding phenol, 2-(*p*-hydroxyphenyl)-2-(*p*-tolyl)-3-(*p*-chlorophenyl)propionitrile, did not possess any detectable activity. Varying the amino side chain to a γ-dimethylamino-*n*-propyl or β-dimethylamino-isopropyl group (see Experimental) notably increased toxicity effects. One example of another structural modification (XXXIII) in the nitrile series was made (see Experimental) and screened for hypocholesterolemic activity. This homolog of the 2,2,3-triarylpropionitriles was orally active only at 0.01% in the diet.



XXXIII

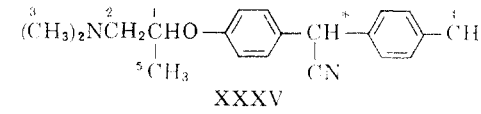
Interestingly, only serum cholesterol levels were reduced at doses as high as 0.10%. No significant lowering was observed in the liver or adrenal.

Partial structure XXXIV represents a moiety common to most of the compounds in this work. Regardless of the nature of the other two substituents on the asterisked carbon (*e.g.*, XXXIV may represent compounds VI, VII, IX, XII, XVII, XIX, etc.) the location of the n.m.r. peaks assigned to the protons on C_1–C_5 remained nearly constant. Structure XXXIV showed a triplet centered at 3.99 ± 0.03 p.p.m. (C_1), a triplet



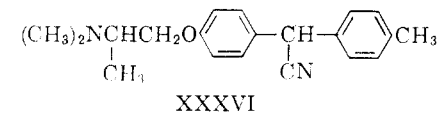
XXXIV

centered at 2.82 ± 0.03 p.p.m. (C_2), a quartet centered at 2.62 ± 0.03 p.p.m. (C_3), a singlet at 2.30 ± 0.03 p.p.m. (C_4), and a triplet centered at 1.06 ± 0.01 p.p.m. (C_5). A proton on C* of structure XXXIV exhibited a singlet located at 4.79 ± 0.01 p.p.m. when XXXIV represents XVII or XIX and at 5.00 p.p.m. in XXXV. Other n.m.r. peaks exhibited by XXXV were as follows: a multiplet centered at about 4.5 p.p.m. (C_1), a doublet centered at about 2.36 p.p.m. (C_2), a singlet at 2.33



XXXV

p.p.m. (C_3), a singlet at 2.27 p.p.m. (C_4), and a doublet centered at 1.25 p.p.m. (C_5). Since the single proton multiplet (C_1) was at lower field than the two-proton doublet (C_2), these results allowed the assignment of structure XXXV rather than XXXVI to the product obtained from the reaction of V with 2-dimethylaminopropyl chloride (see Experimental). Despite excellent yields of noncrystalline aminonitrile hydrochloride obtained in this reaction, only 10–15% yields of crystalline XXXV were isolated. The bulk of the material could not be further purified in our hands. Compound XXXV should be formed in significantly lesser yield than XXXVI from the intermediate unsymmetrical iminium ion. Since both XXXV and XXXVI contain two asymmetric centers, the reaction product should contain 4 racemic compounds. We have evidently succeeded in crystallizing the hydrochloride of only one of these 4 compounds.



XXXVI

Experimental[10]

***p*-Benzoyloxyphenyl-*p*-tolylacetonitrile (V).**—This compound was obtained in 65–70% yields from *p*-benzoyloxybenzaldehyde (IV), toluene, boron trifluoride, and hydrocyanic acid according to the general procedure of Mills.[4] The product crystallized from ethanol, m.p. 118–119°.

Anal. Calcd. for $C_{22}H_{17}NO_2$: C, 80.71; H, 5.23; N, 4.28. Found: C, 80.56; H, 5.24; N, 4.19.

***p*-Chlorobenzyloxyphenyl-*p*-tolylacetonitrile (XIVa).**—To 5.73 g. (147 mmoles) of freshly prepared sodamide suspended in 400 ml. of dry toluene was added 43.8 g. (134 mmoles) of the diarylacetonitrile (V). After heating the mixture 1.5 hr. at 60°, during which time the reaction mixture acquired a blue-green color, 25 g. (155 mmoles) of *p*-chlorobenzyl chloride was added. After stirring and heating the mixture overnight at 60°, it was brought to reflux for 1 hr., then cooled and washed successively with 10% sodium hydroxide, water, and brine. After drying over calcium chloride, the solvents were removed *in vacuo*, leaving 45 g. of oil. Crystals from ethanol melted at 72–76°. Two further recrystallizations from ether–petroleum ether gave 21.5 g., m.p. 83–84°.

Anal. Calcd. for $C_{22}H_{18}ClNO$: C, 75.96; H, 5.22; N, 4.03; Cl, 10.19. Found: C, 75.71; H, 5.58; N, 3.89; Cl, 9.96.

2-(*p*-Chlorobenzyloxyphenyl)-2-*p*-tolyl-3-*p*-chlorophenylpropionitrile (XVa).—Compound XIVa was retreated in the same manner with *p*-chlorobenzyl chloride and sodamide to furnish XVa, m.p. 107–109°, in 60% yield.

Anal. Calcd. for $C_{29}H_{23}Cl_2NO$: C, 73.73; H, 4.90; Cl, 15.01; N, 2.96. Found: C, 73.69; H, 4.83; Cl, 15.10; N, 2.90.

***p*-Benzyloxyphenyl-*p*-tolylacetonitrile (XIVb).**—After adding 19.28 g. (59 mmoles) of *p*-benzoyloxyphenyl-*p*-tolylacetonitrile (V) to a solution of 1.43 g. (62 mmoles) of sodium in 75 ml. of ethanol, the mixture was refluxed for 1 hr. Then 9.42 g. (74.4 mmoles) of benzyl chloride was added and refluxing continued for 1.5 hr. After cooling, the reaction mixture was diluted with water and extracted with chloroform. The extracts were washed with water and brine and dried over anhydrous magnesium sulfate. The solvent was removed *in vacuo* to furnish 28 g. of yellow solid. Two recrystallizations of the product from acetone–

(8) Screening for oral activity in hyperchlolesterolemic rats was carried out according to the method of R. G. Herrmann, C. C. Lee, and R. Parker, *Arch. Intern. Pharmacodyn.*, **133**, 284 (1961). The active nitriles reduced serum, liver, and adrenal cholesterol levels. However, there appeared to be less effect on adrenal levels than with triparanol. This could be a desirable factor in a hypocholesterolemic agent since there might be lesser likelihood of disturbing normal adrenal function. No data are available on the sensitivity of this assay method to other sterols, or on the presence or absence of other sterols in the serum and tissues of the treated animals.

(9) Screening of the compounds for cholesterol lowering activity by the subcutaneous route was carried out on normocholesterolemic, weanling male rats on a normal diet. The rats were injected with a 1 or 3 mg. daily dose for 12 days. A blood sample was withdrawn at the time of sacrifice and the serum analyzed for cholesterol content. No tissue analyses were made. Since the rats averaged about 100 g. in weight during the course of the test, the dosage data can be converted to a mg./kg. basis by multiplying the dose times 10. Dose levels in the 2 tests can be roughly interrelated. A s.c. 3 mg./rat dose equals 30 mg./kg., and an oral 0.05% dose equals approximately 36 mg./kg. as estimated by measurement of food consumption.

(10) All melting points are corrected. Ultraviolet, infrared, and n.m.r. spectra were obtained in ethanol, chloroform, and deuteriochloroform, respectively. Titrations were carried out in a 66% aqueous dimethylformamide system. All ultraviolet spectra obtained were consistent with a summation spectrum of the contributing aryl groups present in the molecule. The n.m.r. spectra integrated correctly for the number of hydrogens in the assigned structures.

petroleum ether gave 14.5 g. (78%) of XIVb, m.p. 122–124°.

Anal. Calcd. for $C_{22}H_{19}NO$: C, 84.31; H, 6.11; N, 4.47. Found: C, 84.53; H, 6.27; N, 4.39.

p-(β-Diethylaminoethoxyphenyl)-p-tolylacetonitrile Hydrochloride (VI·HCl).—To 1.95 g. (85 mmoles) of sodium dissolved in 100 ml. of ethanol was added 26.2 g. (80 mmoles) of V, and the solution was refluxed for 1 hr. and then cooled. In the meantime, 17.2 g. (100 mmoles) of β-diethylaminoethyl chloride hydrochloride was converted to the free base in the usual manner. The ethereal solution of the free base was dried over magnesium sulfate and the solution then filtered directly into the cooled reaction flask. Heating was resumed, and after most of the ether had evaporated the reaction mixture was refluxed for 1 hr. It was poured into water and extracted several times with ether. The ethereal solution was washed successively with 10% sodium hydroxide, water, and brine. After drying over sodium carbonate, the ether was evaporated *in vacuo* to yield 40 g. of oil. This was redissolved in ether and the product converted to its hydrochloride. Evaporation of the ether decanted from the hydrochloride gum gave 10.17 g. of ethyl benzoate. The gum was digested with ethyl acetate to give crystals melting at 114–118°, 26.42 g. (92%); pK_a 5.78; mol. wt., calcd.: 359, found: 354.

Anal. Calcd. for $C_{21}H_{26}ClN_2O\cdot HCl$: C, 70.27; H, 7.58; Cl, 9.88; N, 7.81. Found: C, 70.18; H, 7.83; Cl, 9.71; N, 7.91.

2-[p-(β-Diethylaminoethoxy)phenyl]-2-(p-tolyl)-3-(p-chlorophenyl)propionitrile Hydrochloride (VII·HCl).—VII was prepared by the same procedure described for the preparation of XIVa above. In this case, of course, VI rather than V served as the starting material and C-alkylation occurred. The resulting product, being an amine, was purified as the hydrochloride. For physical constants see Table I. Other analogs similarly prepared from VI in a toluene solvent are denoted in Table I by 't'.

2-p-Benzyloxyphenyl-2-p-tolyl-3-p-chlorophenylpropionitrile (XVb).—Twenty grams (64 mmoles) of XIVb was added to sodamide, prepared from 1.61 g. (70.3 mmoles) of sodium, in liquid ammonia. After about 10 min. 11.30 g. (70.3 mmoles) of p-chlorobenzyl chloride in ether was rapidly added. After 20 min. stirring, the mixture was diluted with ether, solid ammonium chloride cautiously added, and the ammonia evaporated. The remaining ethereal solution was washed with water, dried, and evaporated leaving a solid which crystallized from acetone–hexane, m.p. 141–143°; yield, 25.90 g. (92.5%). An analytical sample melted at 142–145°.

Anal. Calcd. for $C_{29}H_{24}ClNO$: C, 79.53; H, 5.52; Cl, 8.10; N, 3.20. Found: C, 79.57; H, 5.63; Cl, 7.84; N, 2.94.

Analogs of VII, which were prepared in a liquid ammonia solvent by a procedure identical with that described for XVb, are denoted in Table I by 'n'. The starting material for these compounds was, of course, VI rather than XIVb, and being amines they were usually purified as their salts.

2-[p-(β-Diethylaminoethoxy)phenyl]-2-(p-tolyl)-3-(p-chlorophenyl)propylamine Dihydrochloride (VIII·2HCl).—Lithium aluminum hydride reduction of 4.48 g. of nitrile VII in refluxing ether gave the diamine VIII, which was converted to the dihydrochloride (4.71 g.), m.p. 155–165°, pK_a 7.25 and 8.30.

Anal. Calcd. for $C_{28}H_{35}ClN_2O\cdot 2HCl$: C, 64.18; H, 7.12; Cl, 20.30; N, 5.35; mol. wt., 524. Found: C, 64.03; H, 7.29; Cl, 20.71; N, 5.19; mol. wt., 540.

N-Acetyl-VIII Dihydrochloride (IX, R_1 = H, R_2 = $COCH_3$).—Compound VIII was dissolved in acetic anhydride and warmed on the steam bath for 3 hr. The acetic anhydride was then removed *in vacuo* and ice water was added to the resulting residue. After ether extraction of the mixture, the organic phase was washed with dilute bicarbonate solution followed successively by water and brine. The ether solution was then dried over magnesium sulfate, filtered, and concentrated to an oil.

The hydrochloride was prepared in ether and recrystallized twice from acetone–ethyl acetate (94% yield). Unexpectedly the salt proved to be a dihydrochloride, m.p. 134–138°; pK_a 8.15; mol. wt., calcd.: 566, found: 555. The second mole of acid titrated as essentially free hydrochloric acid, because of its weak bonding to the amide group in solution. After drying the product overnight over potassium hydroxide pellets *in vacuo*, 0.8 of an equivalent of "free" hydrochloric acid was titrated. Drying over potassium hydroxide pellets *in vacuo* at 80° for 2 hr. reduced the "free" hydrogen chloride content to 0.4 equiv. The sample for elemental analysis and titration was prepared by vacuum drying at room temperature.

Anal. Calcd. for $C_{30}H_{37}ClN_2O_2\cdot 2HCl$: C, 63.66; H, 6.95; Cl, 18.79; N, 4.95. Found: C, 63.78; H, 7.17; Cl, 17.29; N, 4.70.

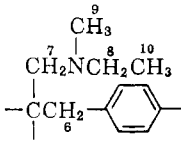
N-Ethyl-2-[p-(β-diethylaminoethoxy)phenyl]-2-(p-tolyl)-3-(p-chlorophenyl)propylamine (IX, R_1 = H, R_2 = C_2H_5).—Attempted reduction of the N-acetyl compound (IX, R_1 = H, R_2 = $COCH_3$) with lithium aluminum hydride in refluxing ether (2 hr.) led to the recovery of starting material. Reduction in refluxing tetrahydrofuran (2 hr.) gave a good yield of the diamine as a colorless oil. Without further purification, the crude product gave excellent infrared and ultraviolet spectra consistent with the desired product and titration showed pK_a' 7.7 and 8.7.

Anal. Calcd. for $C_{30}H_{39}ClN_2O$: mol. wt., 479. Found: mol. wt., 472.

N-Methyl-N-ethyl-2-[p-(β-diethylaminoethoxy)phenyl]-2-(p-tolyl)-3-(p-chlorophenyl)propylamine Dihydrochloride (IX, R_1 = CH_3, R_2 = $C_2H_5\cdot 2HCl$).—To 1.39 g. of the N-ethyl compound (IX, R_1 = H, R_2 = C_2H_5) was added 5 ml. of 98–100% formic acid and 5 ml. of 37% formaldehyde. After refluxing for 6 hr., the solution was diluted with ether and washed with 5% sodium hydroxide and then with water. Evaporation of the dried ether gave 1.11 g. of oil which was converted to the dihydrochloride. Crystals obtained in 44.5% yield from ethyl acetate melted at 193–198° C., pK_a' 6.7 and 8.1.

Anal. Calcd. for $C_{31}H_{41}ClN_2O$: mol. wt., 565. Found: mol. wt., 568.

The n.m.r. spectrum of the product showed, in addition to the peaks discussed for partial structure XXXIV, singlets located at 3.05 p.p.m. (C_6) (see XXXVII), 2.80 p.p.m. (C_7), and at 1.78



XXXVII

p.p.m. (C_9), a quartet centered at 2.14 p.p.m. (C_8), and a triplet centered at 0.86 p.p.m. (C_{10}).

N,N-Dimethyl-2-[p-(β-diethylaminoethoxy)phenyl]-2-(p-tolyl)-3-(p-chlorophenyl)propylamine Dihydrochloride (IX, R_1 = R_2 = $CH_3\cdot 2HCl$).—In the same manner as described above the primary amine (VIII) was converted to the dimethyl compound (IX, R_1 = R_2 = CH_3) with formic acid and formaldehyde and purified as the dihydrochloride, (48.5% yield) m.p. 205–225° dec. (methanol–ethyl acetate–ether), pK_a 6.45 and 7.75.

Anal. Calcd. for $C_{30}H_{39}ClN_2O\cdot 2HCl$: C, 65.27; H, 7.49; ionic Cl, 12.85; N, 5.08; mol. wt., 552. Found: C, 65.89; H, 7.58; ionic Cl, 12.79; N, 4.85; mol. wt., 582.

2-[p-(β-Diethylaminoethoxy)phenyl]-2-(p-tolyl)-3-(p-chlorophenyl)propanal (XII) and - propanol (XIII).—A solution of 3.4 g. (7.6 mmoles) of diamine (VIII) and 1.13 g. (8.5 mmoles) of finely ground N-chlorosuccinimide in 200 ml. of methylene chloride was allowed to stand 0.5 hr. at room temperature and then over the weekend in the refrigerator. The mixture was then diluted with ether and filtered from some solid succinimide. The ethereal solution was washed with water and dried over sodium sulfate. Solvents were carefully evaporated *in vacuo* at room temperature or below, leaving an oil which showed N–H absorption in the infrared region at 3.04 μ compared to the 2.94 μ peak of the starting amine. The oil was dissolved in a solution of 1.8 g. of sodium in 250 ml. of ethanol and warmed on the steam bath for 45 min., causing a precipitate of sodium chloride to form. The ethanol solution was then made strongly acidic with *N* sulfuric acid and stirred a few hr. at room temperature. The clear solution was poured onto ice and made basic with sodium carbonate. Extraction of the basic mixture with ether, followed by washing, drying, and concentration of the ethereal extracts *in vacuo*, left 3.56 g. of oil with infrared peaks at 3.65 μ and 5.80 μ indicative of the aldehyde grouping.

The 3.56 g. of crude aldehyde (XII) was reduced with lithium aluminum hydride in ether to yield 3.0 g. of oil which crystallized upon trituration with petroleum ether. Two recrystallizations from the same solvent gave material melting at 109–110°. A third recrystallization gave an analytical sample of XIII, m.p. 111–112°.

Anal. Calcd. for $C_{28}H_{34}ClNO_2$: C, 74.40; H, 7.58; Cl, 7.84; N, 3.10. Found: C, 74.67; H, 7.65; Cl, 7.96; N, 2.99.

A sample of the aldehyde XII from another preparative run was purified for pharmacological testing. Since neither the free base nor its hydrochloride was crystalline, the compound was purified by

chromatography on alumina. A colorless oil was obtained, λ_{max} 276 (2710); pK_a 8.15; mol. wt., calcd.: 449, found: 453. In addition to the n.m.r. peaks located as discussed for partial structure XXXIV, the aldehyde XII gave singlets at 3.58 p.p.m. (the C-3 methylene bearing the *p*-chlorophenyl) and at 9.7 p.p.m. (CHO).

2-(*p*-Hydroxyphenyl)-2-(*p*-tolyl)-3-(*p*-chlorophenyl)propionitrile (Ether Cleavage of XVb).—Seven grams of XVb in 200 ml. of acetic acid and 150 ml. of 47% hydrobromic acid was refluxed for 2 hr. Upon cooling the reaction mixture, a solid formed which was filtered on a Büchner and washed with water. Vacuum drying in a desiccator gave 6.0 g. of an oily solid, m.p. 143–146°. Three recrystallizations from ethyl acetate–hexane raised the m.p. to 153–156° (77.7% yield), pK_a 11.9.

Anal. Calcd. for $C_{22}H_{18}ClNO$: C, 75.96; H, 5.22; Cl, 10.19; N, 4.03; mol. wt., 348. Found: C, 76.17; H, 5.35; Cl, 10.11; N, 3.78; mol. wt., 354.

2-[*p*-(β-Diethylaminoethoxy)phenyl]-2-(*p*-chlorobenzyl)-3-(*p*-chlorophenyl)propionitrile Hydrochloride (XXXIII·HCl).—2-(*p*-Methoxyphenyl)-2-(*p*-chlorobenzyl)-3-(*p*-chlorophenyl)-propionitrile[11] was cleaved to the phenol in the same manner as described above for XVb. The crude product melted at 105–129° and its ultraviolet spectrum showed the shift expected of a phenol upon addition of alkali.

The conversion of 3.06 g. of the phenol to 3.02 g. of amino ether hydrochloride (XXXIII·HCl) was carried out as recorded for VI·HCl above, m.p. 184–187°, pK_a' 7.77.

Anal. Calcd. for $C_{28}H_{30}Cl_2N_2O$·HCl: C, 65.20; H, 6.13; Cl, 19.59; N, 5.30; mol. wt., 518. Found: C, 64.93; H, 6.04; Cl, 20.54; N, 5.41; mol. wt., 517.

***p*-Benzoyloxyphenyl-*p*-tolylacetamide (XVI).**—During the work-up of a mole-scale preparation of V the mother liquors were dissolved in hot benzene in preparation for chromatography. Upon cooling the benzene to room temperature, crystals of XVI precipitated in about 5% yield. The material was crystallized from ethanol, m.p. 186–188°, infrared: 2.94 μ and 3.14 μ (—CO*N*H_2) and 6.04 μ (—*C*O*N*H$_2$).

Anal. Calcd. for $C_{22}H_{19}NO_3$: C, 76.50; H, 5.54; N, 4.06. Found: C, 76.40; H, 5.65; N, 4.12.

***p*-(β-Diethylaminoethoxy)phenyl-*p*-tolylacetamide (XVII) (a).**—A suspension of 1.8 g. (5 mmoles) of VI·HCl in 15 ml. of concd. hydrochloric acid was stirred and heated to 50°. Solution took place in 5–10 min., but the reaction was maintained at 50° for 2 hr. The solution was then cooled, ice added, and the mixture made basic with sodium hydroxide. After extraction with ether–chloroform (3:1), the extracts were washed with water, dried over sodium sulfate, and concentrated *in vacuo* to 1.7 g. of semi-solid yellowish product. Crystallization from acetone–petroleum ether gave m.p. 121–123°; one recrystallization raised this to 127–128°. Yields in this reaction were in the range of 60–75%. This material was identical in all respects with the product (described in b) obtained from the reaction of diethylaminoethyl chloride with the amide XVI obtained as a by-product in the preparation of V.

(**b**).—Substance XVI was converted to XVII by a procedure identical with that described for the preparation of VI. The acetamide (XVII) melted at 128–129° (from hexane), pK_a' 8.6. The n.m.r. spectrum was consistent with the structure assigned.

(11) This compound was kindly provided by Mrs. J. Mills, m.p. 98–99°. *Anal.* Calcd. for $C_{28}H_{19}ClNO$: C, 69.70; H, 4.83; Cl, 17.89. Found: C, 69.71; H, 5.04; Cl, 18.44. It was prepared from two equivalents of *p*-chlorobenzyl chloride and one equivalent of *p*-methoxyphenylacetonitrile by the general method reported for XIVa.

Anal. Calcd. for $C_{21}H_{28}N_2O_2$: C, 74.08; H, 8.29; N, 8.23; mol. wt., 341. Found: C, 74.19; H, 8.30; N, 8.21; mol. wt., 342.

N-(*p*-Chlorobenzyl)-*p*-(β-diethylaminoethoxy)phenyl-*p*-tolylacetamide (XIX).—Treatment of the primary amide XVII with sodamide and *p*-chlorobenzyl chloride in toluene as described for the preparation of XIVa gave the N-substituted amide XIX in 25.8% yield, m.p. 92–93°; pK_a' 8.18; mol. wt., calcd.: 465, found: 502. Infrared: 2.92 μ (NH), 6.0 μ and 6.64 μ (—*C*O*N*H—).

In addition to the n.m.r. peaks discussed with regard to partial structure XXXIV, XIX exhibits a doublet centered at 4.30 p.p.m. (the methylene of the *p*-chlorobenzyl group split by the amide NH).

***p*-(β-Dimethylaminoisopropoxy)phenyl-*p*-tolylacetonitrile Hydrochloride (XXXV·HCl).**—The method of preparation was identical to that described for VI·HCl except that 2-dimethylaminopropyl chloride was used in place of diethylaminoethyl chloride. The resulting hydrochloride melted at 195–202° (from ethyl acetate), pK_a' 7.90.

Anal. Calcd. for $C_{20}H_{24}N_2O$·HCl: C, 69.65; H, 7.31; N, 8.12; mol. wt., 344. Found: C, 69.54; H, 7.29; N, 8.03; mol. wt., 345.

2-[*p*-(β-Dimethylaminoisopropoxy)phenyl]-2-(*p*-tolyl)-3-(*p*-chlorophenyl)propionitrile Hydrochloride.—The title compound was prepared in 79.5% yield from *p*-(β-dimethylaminoisopropoxy)phenyl-*p*-tolylacetonitrile (XXXV) by alkylation in liquid ammonia as described for the preparation of XVb. Crystals of the hydrochloride (from ethyl acetate–ether) melted at 195–205°, pK_a' 7.70.

Anal. Calcd. for $C_{27}H_{29}ClN_2O$·HCl: C, 69.08; H, 6.44; Cl, 15.11; N, 5.97; mol. wt., 470. Found: C, 69.26; H, 6.54; Cl, 15.46; N, 5.73; mol. wt., 484.

2-[*p*-(γ-Dimethylaminopropoxy)phenyl]-2-(*p*-tolyl)-3-(*p*-chlorophenyl)propionitrile Oxalate.—This amino side-chain homolog of VII was prepared from 2-(*p*-hydroxyphenyl)-2-(*p*-tolyl)-3-(*p*-chlorophenyl)propionitrile by treatment with sodium ethoxide and γ-dimethylaminopropyl chloride. Due to the use of the less reactive amino chloride, the mixture was allowed to reflux overnight. (*cf.* VI.) The product was purified as the oxalate (57.4% yield), m.p. 102–104°, pK_a 8.60.

Anal. Calcd. for $C_{27}H_{29}ClN_2O \cdot C_2H_2O_4$: C, 66.59; H, 5.97; N, 5.36; mol. wt., 523. Found: C, 66.45; H, 6.06; N, 5.24; mol. wt., 538.

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