We now have shown that these same insoluble cation exchange resins are effective in the liberation of sugars from sugars anilides and acids from their phenylhydrazides. The use of a cation exchange resin has certain advantages over mineral acid inasmuch as the reaction proceeds smoothly, it can be done on a micro-scale, the yield of product is essentially quantitative, and furthermore the base liberated in the reaction is absorbed completely by the resin thus facilitating the isolation of the desired sugar or sugar acid.

Experimental

Hydrolysis of Anilides.—The general procedure was as follows: A suspension of the sugar anilide (0.05–0.1 g.) and the cation exchange resin (Amberlite IR 120)[5] (0.5 g.) in water (10 ml.) was refluxed until the anilide had gone into solution and the rotation became constant. This required from 20 minutes to one hour. The addition of 10 to 20% ethanol decreased the time required to solubilize the anilide. The resin was removed by filtration and the colorless solution concentrated *in vacuo* to a sirup which was crystallized if possible in the usual way. Some typical results are quoted in Table I.

TABLE I

Anilide	Wt., mg.	Sugar regenerated: Wt., mg.	Yield %	M.p., °C.	$[\alpha]_D^{H_2O}$ (equil.)	Ref.
2,3,4,6-Tetra-*O*-methyl-D-glucose	80	56.5	93	88	+ 83°	6
2,3,4,6-Tetra-*O*-methyl-D-galactose	100	41	54[a]	Liquid	+108	7, 8
2,4-Di-*O*-methyl-D-galactose	117	88.5	95	90–91 (hydrate)	+ 82	9
D-Galactose	108	71.3	94	166	+ 77.5	10

[a] This was the yield of distilled product. Prior to distillation the yield was almost quantitative.

By the same procedure, the anilides of 2,3,4-tri-*O*-methyl-D-galactose, 2,4,6-tri-*O*-methyl-D-galactose, 2,3,4-tri-*O*-methyl-L-rhamnose and 2,4-di-*O*-methyl-D-arabinose have been converted into the parent methyl sugars.

Hydrolysis of Sugar Acid Phenylhydrazides.—The same reaction can be employed for the regeneration of sugar acids and their *O*-methyl derivatives from the corresponding phenylhydrazides. For example, 2,3,6-tri-*O*-methyl-D-mannonic acid was obtained readily from its phenylhydrazide and crystallized as the lactone,[11] m.p. 83–84°, $[\alpha]^{22}D$ +68° (water, *c* 1). The time for the hydrolysis of the phenylhydrazides is somewhat longer.

(5) Product of Rohm and Haas Co., Philadelphia, Pa.
(6) T. Purdie and J. C. Irvine, *J. Chem. Soc.*, **85**, 1049 (1904).
(7) J. C. Irvine and A. Cameron, *ibid.*, **85**, 1071 (1904).
(8) W. N. Haworth and C. W. Long, *ibid.*, 544 (1927).
(9) F. Smith, *ibid.*, 1724 (1939).
(10) Polarimetry, Saccharimetry and the Sugars, p. 717, U. S. Govt. Print. Office, Circular C440, 1942.
(11) F. Smith, THIS JOURNAL, **70**, 3249 (1948).

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Unsymmetrically N-Substituted Piperazines. VIII. Amide Derivatives[1]

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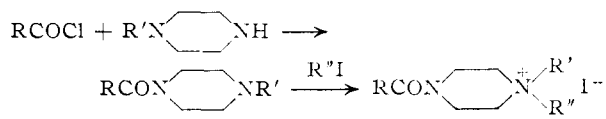
RECEIVED JANUARY 27, 1955

In a search for compounds having anti-acetylcholine activity, a number of quaternary salts derived from N-monoacylpiperazines were prepared. The general synthetic route was



Compound V was prepared by catalytic debenzylation of the benzyl tertiary amine IV. Compound XI was obtained from the base of V by refluxing with excess ethyl iodide in the presence of potassium carbonate.

In most cases the tertiary amines were isolated and characterized as the hydrochlorides. These salts showed little or no physiological activity and were not investigated intensively. The quaternary salts XV–XVIII showed appreciable atropine-like activity (20–200% of atropine when tested on isolated guinea pig ileum) and are being examined with a view to possible chemical trial.

Experimental

Diphenylacetic acid and β,β-diphenylpropionic acid were obtained from commercial sources. 1-Phenylcyclohexanecarboxylic acid[2] (for compounds XII–XV), xanthene-9-carboxylic acid[3] and N-methylpiperazine[4] were prepared by literature methods. N-Ethylpiperazine was prepared by a modification of the Moore procedure.[5] Since this variation offers some practical conveniences it is given in detail.

N-Ethylpiperazine.—In a 3-l. flask was placed 159 g. (1 mole) of piperazine dihydrochloride (recovered from previous operations), 200 cc. of water and 84 g. (1 mole) of sodium bicarbonate. The solution was warmed until the carbon dioxide had been driven off and 1 l. of alcohol was added. To the stirred refluxing solution was added 156 g. (1 mole) of ethyl iodide[6] and 84 g. of solid sodium bicarbonate. The solution was allowed to reflux overnight. It then was cooled and 84 g. of sodium bicarbonate was stirred in while 100 cc. (113 g., 1.05 moles) of ethyl chlorocarbonate was added. After standing an hour the solution was acidified to congo paper with hydrochloric acid and the solvent was removed *in vacuo*. Water was added to dissolve the salts and dicarbethoxypiperazine (70.7 g., 31%) was removed by extraction with ether. To the aqueous layer was added cracked ice and 200 cc. of 40% potassium hydroxide solution. The bases were extracted with ether and dried over potassium carbonate. Fractional distillation afforded 10 g. (7%) of diethylpiperazine and 71 g. (38%) of N-ethyl-N'-carbethoxypiperazine[5] (b.p. 127–130° at 17 mm.).

The carbethoxyethyl piperazine was refluxed 30 hours with 120 cc. of water and 180 cc. of concd. hydrochloric acid and the solution was evaporated *in vacuo*. The residue was dissolved in methanol, neutralized with sodium methylate (from 9 g. of sodium) filtered from salt, and distilled at atmospheric pressure under a fractionating column. There was obtained 34 g. (30% from piperazine) of N-ethylpiperazine, boiling at 126–129°.

N-(β,β-Diphenylpropionyl)-N'-benzylpiperazine (IV).—Six grams of benzylpiperazine[7] was added to a solution of β,β-diphenylpropionyl chloride in 50 cc. of anhydrous ether. There was considerable evolution of heat and solid separated. The mixture was allowed to stand overnight and then filtered. The solid was washed with benzene and recrystallized from aqueous alcohol. It melted at 255° and at 236–240° when mixed with benzylpiperazine dihydrochloride.[7] The yield was 8.5 g. (63%).

(1) The work here reported is part of a joint project with the Pharmacology Department of these laboratories.
(2) C. H. Tilford, M. G. Van Campen, Jr., and R. S. Shelton, THIS JOURNAL, **69**, 2902 (1947).
(3) W. S. Ide, E. Lorz and R. Baltzly, *ibid.*, **76**, 1122 (1954).
(4) L. P. Albro, R. Baltzly and A. P. Phillips, *J. Org. Chem.*, **14**, 771 (1949).
(5) T. S. Moore, M. Boyle and V. M. Thorn, *J. Chem. Soc.*, 39 (1929).
(6) Ethyl sulfate presumably could be substituted.
(7) R. Baltzly, J. S. Buck, E. Lorz and W. Schoen, THIS JOURNAL **66**, 263 (1944).

TABLE I

DERIVATIVES OF MONOACYLPIPERAZINES $\left(RCON\langle\rangle N^{+}\langle R'\ R''\ X^{-}\right)$

Compound	R	R'	R''	X	M.p., °C.	Empirical Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
I	Ph_2CH	Me	H	Cl	265 d.[b,h]	$C_{19}H_{23}ClN_2O$	69.0	68.4	7.0	6.8
II	Ph_2CH	Me	Me	I	223.5[b,h]	$C_{20}H_{25}IN_2O$	55.1	54.6	5.7	5.6
III	Ph_2CH	Me	Et	I	228[b,h]	$C_{21}H_{27}IN_2O$	56.0	56.1	6.0	6.3
IV	Ph_2CHCH_2	$PhCH_2$	H	Cl	255[c]	$C_{26}H_{29}ClN_2O$	74.2	73.7	7.0	6.7
V	Ph_2CHCH_2	H	H	Cl	224[c]	$C_{19}H_{23}ClN_2O$	69.0	68.7	7.0	7.2
VI	Ph_2CHCH_2	Me	H	Cl	264 d.[c,f]	$C_{20}H_{25}ClN_2O$	69.6	69.8	7.3	7.2
VII	Ph_2CHCH_2	Me	Me	I	260[c]	$C_{21}H_{27}IN_2O$	56.0	55.4	6.0	6.0
VIII	Ph_2CHCH_2	Me	Et	I	218[c]	$C_{22}H_{29}IN_2O$	56.9	57.0	6.3	6.3
IX	Ph_2CHCH_2	Me	*i*-Pr	I	198[b]	$C_{23}H_{31}IN_2O$	57.7	57.5	6.5	6.5
X	Ph_2CHCH_2	Me	*n*-C_4H_9	I	223[c]	$C_{24}H_{33}IN_2O$	58.5	58.3	6.8	6.8
XI	Ph_2CHCH_2	Et	Et	I	235[c]	$C_{23}H_{31}IN_2O$	57.7	57.1	6.5	6.5
XII	$(CH_2)_5CPh$-	Me	H	Cl	268[b,g]	$C_{18}H_{27}ClN_2O$	66.9	67.0	8.4	8.4
XIII	$(CH_2)_5CPh$-	Me	Me	I	248[d]	$C_{19}H_{29}IN_2O$	53.3	53.0	6.8	7.0
XIV	$(CH_2)_5CPh$-	Me	Et	I	206[d]	$C_{20}H_{31}IN_2O$	54.3	54.1	7.1	7.0
XV	$(CH_2)_5CPh$-	Me	*i*-Pr	I	172[b]	$C_{21}H_{33}IN_2O$	55.2	55.0	7.3	7.5
XVI	$C_{13}H_9O$[a]	Me	Et	I	244 d.[e]	$C_{21}H_{25}IN_2O_2$	54.3	54.2	5.4	5.6
XVII	$C_{13}H_9O$[a]	Et	Et	I	246 d.[e]	$C_{22}H_{27}IN_2O_2$	55.2	55.3	5.7	5.8
XVIII	$C_{13}H_9O$[a]	Me	*i*-Pr	I	256 d.[e]	$C_{22}H_{27}IN_2O_2$	55.2	55.7	5.7	5.8

[a] 9-Xanthenyl. [b] Crystallized from abs. ethanol. [c] Crystallized from aqueous ethanol. [d] Crystallized from ethanol–ether mixtures. [e] Crystallized from methanol. [f] The base crystallizes from benzene–hexane and melts at 98°. [g] The base melts at 96–98°. [h] Reported after the conclusion of this work by O. Hromatka, O. Kraupp and L. Stentzel, *Monatsh.*, **85**, 1208 (1954).

N-(β,β-Diphenylpropionyl)-piperazine (V).—The above hydrochloride was dissolved in 50 cc. of aqueous alcohol (95% ethanol + aq. hydrochloric acid) and hydrogenated over palladized charcoal. The reduction was slow and it was necessary to heat to about 60°. The hydrogen absorption was 22 mmoles (calcd. 20). The solution was removed from the catalyst, evaporated *in vacuo* and the solid residue was recrystallized from aqueous alcohol (yield 4.5 g.). This hydrochloride apparently retains moisture with great obstinacy and correct analytical figures could not be obtained directly. Those given in the table were obtained by correcting for moisture content: air-dried material was used in the combustion and a larger portion (100 mg.) of the same sample was dried at 0.02–0.04 mm. at 98°. The correction for moisture (4.3%) then was applied to the combustion figures.

N-(β,β-Diphenylpropionyl)-N'-diethylpiperazinium Iodide (XI).—Three grams of the secondary amine hydrochloride (V) was converted to the base. To this was added 3 cc. of ethyl iodide in 20 cc. of methanol, 6 g. of potassium carbonate and 5 cc. of water. The solution was refluxed 34 hours and the methanol was evaporated. The residue was washed with ether, filtered and the solid precipitate was washed with a little cold water. It was recrystallized from aqueous alcohol.

The N'-Methylpiperazine Amide of 1-Phenylcyclohexanecarboxylic Acid (XII).—In 20 cc. of dry benzene were dissolved 7.4 g. of 1-phenylcyclohexanecarboxylic acid chloride (0.033 mole) and 6.6 g. of methylpiperazine (0.066 mole). The reaction mixture was refluxed for 10 hours, cooled and partitioned between water and ether. The ethereal layer was then extracted with dilute hydrochloric acid from which 9.2 g. of water-insoluble base was precipitated by alkali. The hydrochloride was prepared by dissolving the base in absolute ethanol and adding a slight excess of ethanolic hydrogen chloride solution.

N-(1-Phenylcyclohexanecarbonyl)-N'-methyl-N'-ethylpiperazinium Iodide (XIV).—To 2.6 g. of the base XII in 20 cc. of acetone was added 25 cc. of 0.5 *M* ethyl iodide solution in ether. The solution was warmed gently on the steam-bath and the precipitated solid was recrystallized from ethanol–ether mixture. Correct analytical figures were obtained only after drying at 98° at 0.02 mm. pressure.

N-(Xanthene-9-carbonyl)-N'-methyl-N'-ethylpiperazinium Iodide (XVI).—One-tenth mole (21 g.) of xanthene-9-carboxylic acid was converted to the acid chloride by refluxing with excess thionyl chloride in benzene. When no more hydrogen chloride was evolved, the solvents were removed *in vacuo*, and the residual oil was dissolved in benzene. To it was added 20 g. of methylpiperazine and the resultant reaction mixture was refluxed one hour. After cooling, the material was partitioned between ether and water. The ethereal layer was then extracted with dilute hydrochloric acid from which the base was precipitated by addition of alkali. The solid base was washed with water and then dissolved in acetone. Excess ethyl iodide was added and the solution was warmed on the steam-bath for 9 hours. An oil had precipitated: the solvent was evaporated and ethanol was added whereupon the oil crystallized. The solid was recrystallized from methanol.

It will be observed that a number of the compounds reported in Table I furnished analytical figures that are not entirely satisfactory. Most of these deficiencies may be attributed to obstinate retention of moisture which is rather common with high-melting piperazine salts. In certain cases (compounds V and XIV above) these difficulties were surmounted. Compound XI may well have contained inorganic impurities.

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2-Phenylpyridines[1a,b]

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RECEIVED DECEMBER 1, 1954

The formation of mono-, di- and trimethylpyridines by the addition of acetonitrile to 1,3-dienes at 400° has been reported in a previous communication.[3] This note reports the results of some experiments extending the work to the synthesis of methyl substituted 2-phenylpyridines by the reaction of benzonitrile with butadiene, isoprene, 2-methylpentadiene and 2,3-dimethylbutadiene, respectively.

(1) (a) Part IX in the series of papers entitled "The Reaction of Cyanogen and Related Nitriles with 1,3-Dienes"; (b) abstracted in part from the thesis submitted by W. J. G. McCulloch in partial fulfillment of the requirements for the degree of Doctor of Philosophy (Chemistry), Rensselaer Polytechnic Institute, Troy, N. Y.

(2) Research Corporation Fellow in Chemistry, 1951–1953.

(3) G. J. Janz and S. C. Wait, Jr., THIS JOURNAL, **76**, 6377 (1954).