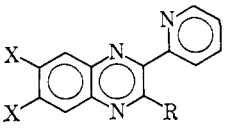
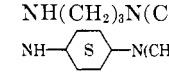
TABLE I

2,6,7-SUBSTITUTED 3-(2-PYRIDYL)QUINOXALINES



No.	X, X	R	Mp, °C	Yield purified, %	Purifcn solvent	Formula	Analyses[a]
1	H, Cl	OH	121–124	70	EtOH–H_2O	$C_{13}H_8ClN_3O$	H, N; C[a]
2	H, Cl	Cl	106–109	65	EtOH–H_2O	$C_{13}H_7Cl_2N_3$	C, H, N
3	H, Cl	$NH(CH_2)_3N(CH_3)_2$	222–225 dec	48	*i*-PrOH	$C_{18}H_{20}ClN_5\cdot 2HCl$	C, H, N
4	H, Cl	$NH(CH_2)_2N(CH_2)_4$	244–246	53	MeOH	$C_{19}H_{20}ClN_5\cdot 2HCl$	C, H, N
5	H, Cl	$NH(CH_2)_2N(C_2H_5)_2$	208–210	88	MeOH–Et_2O	$C_{19}H_{22}ClN_5\cdot 2HCl$	C, H, N
6	H, Cl	$NH(CH_2)_3N(CH_2)_4$	110–112 dec	19	*i*-PrOH–Et_2O	$C_{20}H_{22}ClN_5\cdot 2HCl$	C, H, N
7	H, Cl		151–153	27	*i*-PrOH–Et_2O	$C_{21}H_{24}ClN_5\cdot 2HCl\cdot 0.9H_2O$	C, H, N, Cl, H_2O
8	Cl, Cl	OH	217–219	50	MeOH	$C_{13}H_7Cl_2N_3O$[b]	C, H, N
9	Cl, Cl	$NH(CH_2)_2N(C_2H_5)_2$	258–259 dec	84	MeOH	$C_{19}H_{21}Cl_2N_5\cdot HCl$	C, H, N
10	Cl, Cl	$NH(CH_2)_3N(CH_2)_4$	233–235 dec	91	MeOH–Et_2O	$C_{20}H_{21}Cl_2N_5\cdot 2HCl$	C, H, N
11	CH_3, CH_3	OH	219–222	35	MeOH	$C_{15}H_{13}N_3O$	H, N; C[c]
12	CH_3, CH_3	Cl	135–137	55	EtOH–H_2O	$C_{15}H_{12}ClN_3$	C, H, N
13	CH_3, CH_3	$NH(CH_2)_3N(CH_3)_2$	248–250	64	EtOH	$C_{20}H_{25}N_5\cdot 2HCl\cdot 1.67H_2O$	C, H, N, H_2O
14	CH_3, CH_3	$NH(CH_2)_2N(C_2H_5)_2$	236–238	63	*i*-PrOH	$C_{21}H_{27}N_5\cdot 2HCl\cdot 0.33H_2O$	C, H, N, H_2O

[a] C: calcd, 60.57; found, 59.72. [b] The chloro compound from **8** was not obtained analytically pure. The crude material, mp 126–130°, was used directly for the next step. [c] C: calcd, 71.69; found, 71.19.

0.1 mole of a substituted *o*-phenylenediamine in 350 ml of 35% H_2SO_4 was stirred at 75° for 18 hr. The solid which formed on heating was removed by filtration and dissolved in H_2O. The solution was adjusted to pH 8 with NH_4OH and the solid which formed was removed by filtration, washed thoroughly with H_2O, and recrystallized to yield the product.

6,7-Substituted 2-Chloro-3-(2-pyridyl)quinoxalines (IV) (Table I).—A slurry of 0.4 mole of a 6,7-substituted 3-(2-pyridyl)-2-quinoxalinol in 200 ml of $POCl_3$ was heated under reflux for 7 hr. The resulting solution was cooled, poured slowly into 4 l. of iced H_2O, and made basic with NH_4OH. The product was removed by filtration and recrystallized.

2-{[(Dialkylamino)alkyl]amino}-3-(2-pyridyl)quinoxalines (V) (Table I).—A solution of 0.01 mole of a 6,7-substituted 2-chloro-3-(2-pyridyl)quinoxaline and 0.02 mole of diamine in 50 ml of Et_2O and 15 ml of C_6H_6 was held at 5° for 24–48 hr. The solid amine hydrochloride which formed was removed by filtration. The ether solution was washed successively with H_2O, dilute NaOH, and H_2O, and then dried over Na_2SO_4. To this solution was added *i*-PrOH saturated with gaseous HCl to give the hydrochloride salt of the product which was removed by filtration and recrystallized.

Acknowledgments.—The authors are indebted to Dr. Leo Rane of the University of Miami and to Dr. Paul E. Thompson and Dr. M. W. Fisher of Parke, Davis and Company for the biological testing. We also wish to thank Mr. C. E. Childs and associates for the microanalyses and Dr. J. M. Vandenbelt and coworkers for determination of the spectral data reported herein.

Antimalarial Agents. I. Reduction of Sydnone Derivatives

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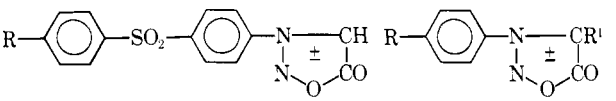
3-{*p*-[(4-Aminophenyl)sulfonyl]phenyl}sydnone (Ia) and other amino-substituted sydnones related to the antimalarial drug bis(*p*-aminophenyl) sulfone (DDS) are of interest to us in our program on antimalarial agents because of their structural relationship to DDS and 3-piperonylsydnone. The latter compound was active against *Plasmodium berghei* in the mouse.[1] The logical way to prepare Ia seemed to be the reduction of 3-{*p*-[(4-nitrophenyl)sulfonyl]phenyl}sydnone (Ib),



Ia, R = NH_2
b, R = NO_2
c, R = AcNH
d, R = Cl

IIa, R = NO_2; R^1 = H
b, R = NH_2; R^1 = H
c, R = NO_2; R^1 = Me
d, R = NH_2; R^1 = Me
e, R = R^1 = H
f, R = HONH; R^1 = H
g, R = AcON(Ac); R^1 = H
h, R = AcNH; R′ = H

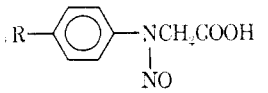
which we had synthesized in an eight-step reaction sequence. Another approach would be the hydrolysis of 3-{*p*-[(4-acetamidophenyl)sulfonyl]phenyl}sydnone (Ic) or the replacement of Cl with NH_2 in 3-{*p*-[(4-chlorophenyl)sulfonyl]phenyl}sydnone (Id). However the sydnone ring of Ic and Id should be opened under the hydrolytic conditions or the amination reaction conditions. Thus the reduction of the nitrosydnone Ib was chosen for the preparation of the aminosydnone Ia. The more readily available 3-(*p*-nitrophenyl)sydnone (IIa) appeared to be a good model for this reduction study before we initiated any work with the nitro compound Ib.

A search of the literature revealed that although 3-(*p*-nitrophenyl)sydnone (IIa) is known, 3-(*p*-aminophenyl)sydnone (IIb) has not been described. Similarly, 3-(*p*-nitrophenyl)-4-methylsydnone (IIc) is known, but 3-(*p*-aminophenyl)-4-methylsydnone (IId) is unknown.

(1) W. H. Hyberg and C. C. Cheng, *J. Med. Chem.*, **8**, 531 (1965).

The sydnone ring is reported to be unstable to reduction. Thus, 3-phenylsydnone (IIe) gave ammonium N-phenylglycinate when it was hydrogenated catalytically.[2] The same fission took place when 3-phenylsydnone was refluxed with zinc and 6.2% AcOH for 15 min.[3] These are relatively mild conditions but apparently severe enough to open the sydnone ring.

3-(*p*-Nitrophenyl)sydnone (IIa) was prepared in better than 90% conversion by the dehydration of N-(*p*-nitrophenyl)-N-nitrosoglycine (IIIa) with trifluoroacetic anhydride. The melting point of the product was somewhat higher than that reported[2,4] but its identity was confirmed by N analysis and ir spectrum.



IIIa, R = NO_2
b, R = NH_2

Qualitative stability tests showed that most of the 3-(*p*-nitrophenyl)sydnone (IIa) can be recovered when refluxed for 5–12 min in 2% AcOH. Thus it was refluxed with Fe powder in 2% AcOH to give 60% of 3-(*p*-aminophenyl)sydnone (IIb), mp 195–196° dec. The identity of this product was confirmed by analysis and ir spectrum; HCl could be substituted for AcOH in this reduction. When a mixture of glacial AcOH and acetic anhydride was used the product obtained was 3-[*p*-(acetamido)phenyl]sydnone (IIh).

3-{*p*-[(4-Aminophenyl)sulfonyl]phenyl}sydnone (Ia) was obtained in good yield when this reduction method was applied to 3-{*p*-[(4-nitrophenyl)sulfonyl]phenyl}-sydnone (Ib). The product was identified by analysis and ir spectrum.

At this point it was of interest to us to investigate the reduction of 3-(*p*-nitrophenyl)sydnone (IIa) with Zn in AcOH although we were aware of Earl's work[3] in which 3-phenylsydnone (IIe) was heated with Zn and 6.2% AcOH for 15 min. We use lower concentration of AcOH and a shorter reaction time. The nitrophenylsydnone IIa was refluxed with Zn dust in 1% AcOH for 6 min to give a solid which melted at 167–168° and contained 21.41% N. The ir spectrum showed absence of peaks for NO_2 and was consistent with the structures of either 3-[*p*-(hydroxylamino)-phenyl]sydnone (IIf) or N-(*p*-aminophenyl)-N-nitrosoglycine (IIIb). The internal deformation mode absorption at 6.1 μ for a primary amino group which has been given variably as 6.06–6.29 μ was, however, absent. This indicated that the compound was not N-(*p*-aminophenyl)-N-nitrosoglycine (IIIb).

Upon acetylation of the new product with Ac_2O the acetyl derivative IIg, mp 171–172° dec, was formed. If the Zn reduction product of IIa was N-(*p*-aminophenyl)-N-nitrosoglycine (IIIb), on treatment with Ac_2O it should have yielded the known 3-[*p*-(acetamido)phenyl]sydnone (IIh), mp 251–253°,[5] and should have shown an ir band around 3 μ characteristic for the N–H stretching absorption of the acetamido group.

Additional proof for the structure of 3-[*p*-(hydroxylamino)phenyl]sydnone (IIf) was obtained by its reduction with Fe in dilute AcOH to 3-(*p*-aminophenyl)-sydnone (IIb).

Testing results are available for four of the products mentioned here. 3-{*p*-[(4-Aminophenyl)sulfonyl]-phenyl}sydnone (Ia) was curative[6] when used at the rate of 80, 160, 320, and 640 mg/kg of mouse infected with *Plasmodium berghei*. The nitro analog Ib was curative at 640 mg/kg. Both compounds were void of toxic effects at the maximum dose of 640 mg/kg. Compounds IIa and IIb were not active; IIb was toxic at 160 mg/kg and 640 mg/kg. DDS was curative at 160, 320, and 640 mg/kg; it was toxic at 320 and 640 mg.

Experimental Section

3-(*p*-Nitrophenyl)sydnone (IIa).—A mixture of 40.2 g (0.179 mole) of N-(*p*-nitrophenyl)-N-nitrosoglycine (IIIa), 500 ml of Et_2O, and 30 ml of trifluoroacetic anhydride was stirred for 2 hr. The solid was collected, washed with ether (three 70-ml portions), and recrystallized from THF to give 34.5 g (93%) of light yellow needles: mp 191–192° dec; lit. mp 184°,[2] 187–188°;[4] ir, 6.55 and 7.5 (NO_2), 5.55 and 5.8 (sydnone carbonyl), 3.2 (sydnone C–H), and 6.18 μ (aromatic). *Anal.* Calcd for $C_8H_5N_3O_4$ (IIa): N, 20.28. Found: N, 20.57.

3-(*p*-Aminophenyl)sydnone (IIb). A.—A mixture of 5.0 g of IIa and 15 g of Fe powder was added to 300 ml of 2% AcOH at 90°; the mixture was refluxed for 12 min and then chilled; 8 g of $NaHCO_3$ was added in small portions and the mixture was filtered. The solid was washed with ice water (three 50-ml portions), air dried, and extracted with boiling THF (four 100-ml portions). The combined extracts were evaporated to dryness *in vacuo* and the residue was recrystallized from THF (Darco)–petroleum ether (bp 60–90°) to give 3.2 g (75%) of a light yellow solid: mp 195–196° dec; ir, 2.9, 3.0, 3.1, and 6.1 (NH_2), 3.2 (sydnone C–H), and 5.75 μ (sydnone CO). *Anal.* Calcd for $C_8H_7N_3O_2$ (IIb): N, 23.72. Found: N, 23.84.

B.—A 51% conversion of IIb was obtained from 2.1 g of IIa when 1% HCl was substituted for 2% AcOH.

3-[*p*-(Acetamido)phenyl]sydnone (IIh).—A stirred mixture of 2.1 g of IIa, 15 ml of Ac_2O, 50 ml of glacial AcOH, and 10 g of Fe powder was heated. When the temperature of the mixture reached about 60° an exothermic reaction ensued (80°). The mixture was held at this temperature for 20 min and allowed to cool to room temperature; the solid was collected and washed with 15 ml of Ac_2O. The residue was washed well (H_2O) and then extracted with DMF (three 30-ml portions). The extract was filtered, diluted with H_2O until turbid, and chilled. The solid was collected and dried to give 1.2 g (55%) of IIh, mp 255–257°, lit.[5] mp 251–253°.

3-{*p*-[(4-Aminophenyl)sulfonyl]phenyl}sydnone (Ia).—To a stirred mixture of 2.3 g of 3-{*p*-[(4-nitrophenyl)sulfonyl]phenyl}-sydnone (Ib) and H_2O (500 ml) at 90° was added 10 g of Fe powder and 12 ml of AcOH, and the mixture was refluxed for 10 min. The mixture was chilled and neutralized with $NaHCO_3$. The collected solid was washed (H_2O), air dried, and extracted with boiling THF (three 100-ml portions). The combined extracts were evaporated to dryness *in vacuo* and the residue was recrystallized from THF–petroleum ether to give 1.41 g (67%) of a light yellow solid: mp 213–215° dec; ir, 2.9, 3.0, 3.1, and 6.13 (NH_2), 3.2 (vw, sydnone C–H), 5.75 and 5.85 (sydnone CO), 6.2 (aromatic), 7.63 and 8.7 μ (SO_2). *Anal.* Calcd for $C_{14}H_{11}N_3O_4S$ (Ia): C, 52.97; H, 3.47; N, 13.25. Found: C, 53.09; H, 3.43; N, 12.95.

3-[*p*-(Hydroxylamino)phenyl]sydnone (IIf).—To 200 ml of stirred 1% AcOH at 95° was added 2 g of IIa and 5 g of Zn dust, and the mixture was refluxed for 6 min. The mixture was chilled and filtered; the solid was washed (H_2O), air dried, and extracted with boiling THF (three 100-ml portions). The combined ex-

(2) W. Baker, W. D. Ollis, and V. D. Poole, *J. Chem. Soc.*, 307 (1949).
(3) J. C. Earl, *Rec. Trav. Chim.*, **75**, 346 (1956).
(4) R. A. Eade and J. C. Earl, *J. Chem. Soc.*, 591 (1946).
(5) R. W. Putter and G. Wolfrom, German Patent 1,057,124 (May 14, 1959); *Chem. Abstr.*, **55**, 7436*d* (1961).
(6) The rating "curative" indicates that at least one of the test animals survived 60 days after treatment with the compound. Deaths occurring within the first 5 days after treatment are attributed to toxicity of the compound. The rodent antimalarial test method was reported by T. S. Osdene, P. B. Russell, and L. Rane, *J. Med. Chem.*, **10**, 431 (1967).

tracts were evaporated to dryness *in vacuo* and the solid residue was recrystallized from THF–petroleum ether to give 1.1 g (54%) of a solid: mp 167–168° dec; ir, 3.05 (s) with shoulders at 3.0 and 3.15 (assigned to NHOH), 5.75 (sydnone CO), and 6.2 μ (aromatic). *Anal.* Calcd for $C_8H_7N_3O_3$ (IIf): N, 21.75. Found: N, 21.41.

3-[*p*-(N,O-Diacetylhydroxylamino)phenyl]sydnone (IIg).—A mixture of 1 g of IIf and 15 ml of Ac_2O was heated at 100° for 3 hr. The reaction mixture was evaporated to dryness under reduced pressure and the residual solid was recrystallized from acetone (Darco)–petroleum ether to give 0.82 g (57%) of a solid: mp 171–173°; ir, 3.2 (sydnone C–H), 5.55 (sydnone CO), 5.73 (O–Ac superimposed by second sydnone CO peak), and 5.9 μ (N–Ac). *Anal.* Calcd for $C_{12}H_{11}N_3O_5$ (IIg): C, 51.98; H, 3.97; N, 15.16. Found: C, 52.15; H, 4.38; N, 15.25.

Reduction of 3-[*p*-(Hydroxylamino)phenyl]sydnone (IIf).—A mixture of 0.5 g of IIf and 2 g of Fe powder was added to 50 ml of 2% AcOH at 95° and refluxed for 12 min. The reaction mixture was worked up as described for IIb, and 0.32 g (70%) of a solid, mp 195–196° dec, was isolated. It was identified as IIb by mixture melting point and ir analysis.

Acknowledgment.—This work was supported by the U. S. Army Medical and Development Command. The screening of the compounds was carried out by Dr. L. Rane of University of Miami, Miami, Fla.

11-Alkylated Steroids. VI. 11β-Hydroxy-11α-methyl-5β-pregnan-20-one

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As part of a continuing study of the chemical and biological properties of 11-alkylated steroids,[1] we prepared a representative 3-deoxypregnane of this series, namely, 11β-hydroxy-11α-methyl-5β-pregnan-20-one. Two convergent syntheses, the one originating with an 11-oxo steroid and the other with an 11β-hydroxy-11α-methyl steroid, established the structure of the product.

3α-Hydroxy-5β-pregnane-11,20-dione[2] was converted to the methanesulfonate, which upon treatment with boiling 2,4,6-trimethylpyridine gave a low-melting solid, difficult to purify, presumed[3] to be largely 5β-pregn-2-ene-11,20-dione. Ketalization of the crude material with ethylene glycol afforded the 20-monoketal, which was treated with ethereal methyllithium. The 20,20-ethylenedioxy-11α-methyl-5β-pregn-2-en-11β-ol thus obtained was converted by catalytic hydrogenation and hydrolysis to the desired 11β-hydroxy-11α-methyl-5β-pregnan-20-one.

A more efficient synthesis was that originating with 11β-hydroxy-11α-methyl-5β-pregnane-3,20-dione,[4] which was converted in good yield to the 3,3-ethylene mercaptal by the use of ethanedithiol and boron trifluoride etherate in glacial acetic acid.[5,6] Hydrogenolysis of this thioketal with Raney nickel[7] in ethanol afforded 11β-hydroxy-11α-methyl-5β-pregnan-20-one in good yield.

Biological Information.—The sedative or mild tranquilizing activity of 11β-hydroxy-11α-methyl-5β-pregnane-3,20-dione[4] in humans was about equivalent to that of an equal dose of meprobamate.[8] The compound was selected for clinical trial on the basis of its activity in mice in the motor activity assay of Dews.[9] In contrast, 11β-hydroxy-11α-methyl-5β-pregnan-20-one was essentially inactive in the Dews assay.

Experimental Section[10]

3α-Hydroxy-5β-pregnane-11,20-dione Methanesulfonate.—A mixture of 25 g of 3α-hydroxy-5β-pregnane-11,20-dione, 100 ml of pyridine, and 16 ml of methanesulfonyl chloride was stirred, with ice-bath cooling, for 3 hr and then poured into ice–water. The crude product was recovered by CH_2Cl_2 extraction and chromatographed over Florisil. Elution with Me_2CO gave 22.67 g of white crystalline product, mp 123–139°, a sample of which was recrystallized several times from Me_2CO–petroleum ether to mp 153–155°, $[\alpha]D$ +120° (*c* 1, $CHCl_3$). *Anal.* ($C_{22}H_{34}O_5S$) C, H, S.

5β-Pregn-2-ene-11,20-dione.—3α-Hydroxy-5β-pregnane-11,20-dione methanesulfonate (22.1 g) was refluxed for 3 hr with 120 ml of 2,4,6-trimethylpyridine and then allowed to stand at room temperature overnight. The mixture was poured into 500 ml of ice-cold 3 *N* H_2SO_4, the product was taken up in CH_2Cl_2, and the CH_2Cl_2 extracts were washed with 1 *N* H_2SO_4 and H_2O. Chromatography on Florisil gave 16.1 g of crude product, mp 76–107°, eluted with 5% Me_2CO–petroleum ether. Recrystallization from petroluem ether gave a low yield of an analytical sample, mp 108–111°, $[\alpha]D$ +84° (*c* 1, Me_2CO). *Anal.* ($C_{21}H_{30}O_2$) C, H, double bond.

20,20-Ethylenedioxy-5β-pregn-2-en-11-one.—Crude 5β-pregn-2-ene-11,20-dione (mp 76–107°, 13.4 g) was refluxed overnight with 40 ml of ethylene glycol, 0.5 g of *p*-toluenesulfonic acid monohydrate, and 200 ml of C_6H_6 through a Dean–Stark trap. After cooling, the mixture was washed with aqueous 4% $NaHCO_3$, dried (Na_2SO_4), and evaporated to an orange oil. Chromatography over Florisil afforded 12.0 g of crude product in the 5% Me_2CO–petroleum ether eluate fractions. Only 2.73 g of product was recovered from a petroleum ether recrystallization. Subsequent recrystallization from acetone–petroleum ether containing a drop of pyridine afforded an analytical sample, mp 143–148°, $[\alpha]D$ +53° (*c* 1, Me_2CO). *Anal.* ($C_{23}H_{34}O_3$) C, H.

11β-Hydroxy-11α-methyl-5β-pregnan-20-one.—Crude 20,20-ethylenedioxy-5β-pregn-2-en-11-one (8.7 g) in 100 ml of C_6H_6 was treated with 200 ml of 0.6 *M* ethereal MeLi at room temperature overnight. Washing with H_2O, followed by evaporation of the organic solution, gave an oil that still showed ir C=O absorption. It was re-treated twice with MeLi to give 9.9 g of partly crystalline 20,20-ethylenedioxy-11α-methyl-5β-pregn-2-en-11β-ol that was not purified, since the recrystallization experience with the earlier unsaturated compounds in this series was unsatisfactory.

Hydrogenation of 6.15 g of the crude ketal that contained some residual 11-ketone was carried out in 250 ml of MeOH, using 0.5 g of PtO_2 at 2200 torr for several hours. The catalyst was filtered off and the filtrate was treated with 25 ml of 1 *N* HCl at room temperature overnight. After removal of the MeOH, the products were taken up in CH_2Cl_2, washed with H_2O, and chromatographed on Florisil (elution with 5% Me_2CO–petroleum ether) to give 1.36 g of 11β-hydroxy-11α-methyl-5β-pregnan-20-one, mp 119–122°, after recrystallization from petroleum ether.

11β-Hydroxy-11α-methyl-5β-pregnane-3,20-dione 3-Ethylene Mercaptal.—11β-Hydroxy-11α-methyl-5β-pregnane-3,20-dione

(1) Preceding paper in this series: G. S. Fonken, *J. Org. Chem.*, **30**, 2095 (1965).

(2) J. von Euw, A. Lardon, and T. Reichstein, *Helv. Chim. Acta*, **27**, 821 (1944).

(3) R. J. Bridgewater and C. W. Shoppee, *J. Chem. Soc.*, 1709 (1953).

(4) G. S. Fonken, *J. Org. Chem.*, **23**, 1075 (1958).

(5) J. W. Ralls and B. Riegel, *J. Am. Chem. Soc.*, **76**, 4479 (1954).

(6) L. J. Fieser, *ibid.*, **76**, 1945 (1954).

(7) R. Mozingo, D. E. Wolf, S. A. Harris, and K. Folkers, *ibid.*, **65**, 1013 (1943).

(8) H. L. Upjohn, private communication.

(9) P. B. Dews, *Brit. J. Pharmacol.*, **8**, 46 (1953).

(10) Melting points were determined on a Fisher-Johns block and not further corrected. Ir spectra were consistent with the structures stated. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.3% of the theoretical values. Petroleum ether refers to a product, bp 60–70°, of the Skelly Corp. called Skellysolve B. Florisil is a synthetic magnesium silicate product of the Floridin Co.